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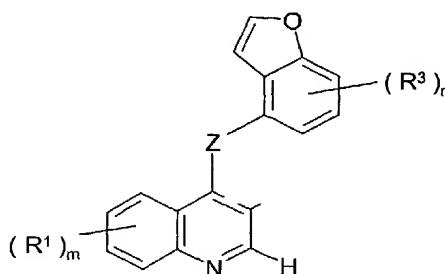
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(54) Title: QUINOLINE DERIVATIVES



(I)

WO 03/047584 A1

(57) Abstract: The invention concerns quinoline derivatives of Formula (I) wherein each of Z, m, R₁, n and R₃ have any of the meanings defined in the description; processes for their preparation, pharmaceutical compositions containing them and their use in the manufacture of a medicament for use as an anti-invasive agent in the containment and/or treatment of solid tumour disease.

QUINOLINE DERIVATIVES

The invention concerns certain novel quinoline derivatives, or pharmaceutically-acceptable salts thereof, which possess anti-tumour activity and are accordingly useful in methods of treatment of the human or animal body. The invention also concerns processes for the manufacture of said quinoline derivatives, to pharmaceutical compositions containing them and to their use in therapeutic methods, for example in the manufacture of medicaments for use in the prevention or treatment of solid tumour disease in a warm-blooded animal such as man.

Many of the current treatment regimes for cell proliferation diseases such as psoriasis and cancer utilise compounds which inhibit DNA synthesis. Such compounds are toxic to cells generally but their toxic effect on rapidly dividing cells such as tumour cells can be beneficial. Alternative approaches to anti-tumour agents which act by mechanisms other than the inhibition of DNA synthesis have the potential to display enhanced selectivity of action.

In recent years it has been discovered that a cell may become cancerous by virtue of the transformation of a portion of its DNA into an oncogene *i.e.* a gene which, on activation, leads to the formation of malignant tumour cells (Bradshaw, Mutagenesis, 1986, 1, 91). Several such oncogenes give rise to the production of peptides which are receptors for growth factors. Activation of the growth factor receptor complex subsequently leads to an increase in cell proliferation. It is known, for example, that several oncogenes encode tyrosine kinase enzymes and that certain growth factor receptors are also tyrosine kinase enzymes (Yarden *et al.*, Ann. Rev. Biochem., 1988, 57, 443; Larsen *et al.*, Ann. Reports in Med. Chem., 1989, Chpt. 13). The first group of tyrosine kinases to be identified arose from such viral oncogenes, for example pp60^{v-Src} tyrosine kinase (otherwise known as v-Src), and the corresponding tyrosine kinases in normal cells, for example pp60^{c-Src} tyrosine kinase (otherwise known as c-Src).

Receptor tyrosine kinases are important in the transmission of biochemical signals which initiate cell replication. They are large enzymes which span the cell membrane and possess an extracellular binding domain for growth factors such as epidermal growth factor (EGF) and an intracellular portion which functions as a kinase to phosphorylate tyrosine amino acids in proteins and hence to influence cell proliferation. Various classes of receptor tyrosine kinases are known (Wilks, Advances in Cancer Research, 1993, 60, 43-73) based on families of growth factors which bind to different receptor tyrosine kinases. The classification

includes Class I receptor tyrosine kinases comprising the EGF family of receptor tyrosine kinases such as the EGF, TGF α , Neu and erbB receptors, Class II receptor tyrosine kinases comprising the insulin family of receptor tyrosine kinases such as the insulin and IGFI receptors and insulin-related receptor (IRR) and Class III receptor tyrosine kinases comprising the platelet-derived growth factor (PDGF) family of receptor tyrosine kinases such as the PDGF α , PDGF β and colony-stimulating factor 1 (CSF1) receptors.

It is also known that certain tyrosine kinases belong to the class of non-receptor tyrosine kinases which are located intracellularly and are involved in the transmission of biochemical signals such as those that influence tumour cell motility, dissemination and invasiveness and subsequently metastatic tumour growth (Ullrich *et al.*, Cell, 1990, 61, 203-212, Bolen *et al.*, FASEB J., 1992, 6, 3403-3409, Brickell *et al.*, Critical Reviews in Oncogenesis, 1992, 3, 401-406, Bohlen *et al.*, Oncogene, 1993, 8, 2025-2031, Courtneidge *et al.*, Semin. Cancer Biol., 1994, 5, 239-246, Lauffenburger *et al.*, Cell, 1996, 84, 359-369, Hanks *et al.*, BioEssays, 1996, 19, 137-145, Parsons *et al.*, Current Opinion in Cell Biology, 1997, 9, 187-192, Brown *et al.*, Biochimica et Biophysica Acta, 1996, 1287, 121-149 and Schlaepfer *et al.*, Progress in Biophysics and Molecular Biology, 1999, 71, 435-478). Various classes of non-receptor tyrosine kinases are known including the Src family such as the Src, Lyn and Yes tyrosine kinases, the Abl family such as Abl and Arg and the Jak family such as Jak 1 and Tyk 2.

It is known that the Src family of non-receptor tyrosine kinases are highly regulated in normal cells and in the absence of extracellular stimuli are maintained in an inactive conformation. However, some Src family members, for example c-Src tyrosine kinase, are frequently significantly activated (when compared to normal cell levels) in common human cancers such as gastrointestinal cancer, for example colon, rectal and stomach cancer (Cartwright *et al.*, Proc. Natl. Acad. Sci. USA, 1990, 87, 558-562 and Mao *et al.*, Oncogene, 1997, 15, 3083-3090), and breast cancer (Muthuswamy *et al.*, Oncogene, 1995, 11, 1801-1810). The Src family of non-receptor tyrosine kinases has also been located in other common human cancers such as non-small cell lung cancers (NSCLCs) including adenocarcinomas and squamous cell cancer of the lung (Mazurenko *et al.*, European Journal of Cancer, 1992, 28, 372-7), bladder cancer (Fanning *et al.*, Cancer Research, 1992, 52, 1457-62), oesophageal cancer (Jankowski *et al.*, Gut, 1992, 33, 1033-8), cancer of the prostate, ovarian cancer (Wiener *et al.*, Clin. Cancer Research, 1999, 5, 2164-70) and pancreatic cancer

(Lutz *et al.*, Biochem. and Biophys. Res. Comm., 1998, 243, 503-8). As further human tumour tissues are tested for the Src family of non-receptor tyrosine kinases it is expected that its widespread prevalence will be established.

It is further known that the predominant role of c-Src non-receptor tyrosine kinase is to 5 regulate the assembly of focal adhesion complexes through interaction with a number of cytoplasmic proteins including, for example, focal adhesion kinase and paxillin. In addition c-Src is coupled to signalling pathways that regulate the actin cytoskeleton which facilitates cell motility. Likewise, important roles are played by the c-Src, c-Yes and c-Fyn non-receptor tyrosine kinases in integrin mediated signalling and in disrupting cadherin-dependent cell-cell 10 junctions (Owens *et al.*, Molecular Biology of the Cell, 2000, 11, 51-64 and Klinghoffer *et al.*, EMBO Journal, 1999, 18, 2459-2471). Cellular motility is necessarily required for a localised tumour to progress through the stages of dissemination into the blood stream, invasion of other tissues and initiation of metastatic tumour growth. For example, colon tumour 15 progression from localised to disseminated, invasive metastatic disease has been correlated with c-Src non-receptor tyrosine kinase activity (Brunton *et al.*, Oncogene, 1997, 14, 283-293, Fincham *et al.*, EMBO J, 1998, 17, 81-92 and Verbeek *et al.*, Exp. Cell Research, 1999, 248, 531-537).

Accordingly it has been recognised that an inhibitor of such non-receptor tyrosine 20 kinases should be of value as a selective inhibitor of the motility of tumour cells and as a selective inhibitor of the dissemination and invasiveness of mammalian cancer cells leading to 25 inhibition of metastatic tumour growth. In particular an inhibitor of such non-receptor tyrosine kinases should be of value as an anti-invasive agent for use in the containment and/or treatment of solid tumour disease.

We have now found that surprisingly certain quinoline derivatives possess potent 25 anti-tumour activity. Without wishing to imply that the compounds disclosed in the present invention possess pharmacological activity only by virtue of an effect on a single biological process, it is believed that the compounds provide an anti-tumour effect by way of inhibition 30 of one or more of the non-receptor tyrosine-specific protein kinases that are involved in the signal transduction steps which lead to the invasiveness and migratory ability of metastasising tumour cells. In particular, it is believed that the compounds of the present invention provide an anti-tumour effect by way of inhibition of the Src family of non-receptor tyrosine kinases, for example by inhibition of one or more of c-Src, c-Yes and c-Fyn.

It is also known that c-Src non-receptor tyrosine kinase enzyme is involved in the control of osteoclast-driven bone resorption (Soriano *et al.*, *Cell*, 1991, 64, 693-702; Boyce *et al.*, *J. Clin. Invest.*, 1992, 90, 1622-1627; Yoneda *et al.*, *J. Clin. Invest.*, 1993, 91, 2791-2795 and Missbach *et al.*, *Bone*, 1999, 24, 437-49). An inhibitor of c-Src non-receptor tyrosine kinase is therefore of value in the prevention and treatment of bone diseases such as 5 osteoporosis, Paget's disease, metastatic disease in bone and tumour-induced hypercalcaemia.

The compounds of the present invention are also useful in inhibiting the uncontrolled cellular proliferation which arises from various non-malignant diseases such as inflammatory 10 diseases (for example rheumatoid arthritis and inflammatory bowel disease), fibrotic diseases (for example hepatic cirrhosis and lung fibrosis), glomerulonephritis, multiple sclerosis, psoriasis, hypersensitivity reactions of the skin, blood vessel diseases (for example atherosclerosis and restenosis), allergic asthma, insulin-dependent diabetes, diabetic retinopathy and diabetic nephropathy.

15 Generally the compounds of the present invention possess potent inhibitory activity against the Src family of non-receptor tyrosine kinases, for example by inhibition of c-Src and/or c-Yes, whilst possessing less potent inhibitory activity against other tyrosine kinase enzymes such as the receptor tyrosine kinases, for example EGF receptor tyrosine kinase and/or VEGF receptor tyrosine kinase. Furthermore, certain compounds of the present 20 invention possess substantially better potency against the Src family of non-receptor tyrosine kinases, for example c-Src and/or c-Yes, than against VEGF receptor tyrosine kinase. Such compounds possess sufficient potency against the Src family of non-receptor tyrosine kinases, for example c-Src and/or c-Yes, that they may be used in an amount sufficient to inhibit, for 25 example, c-Src and/or c-Yes whilst demonstrating little activity against VEGF receptor tyrosine kinase.

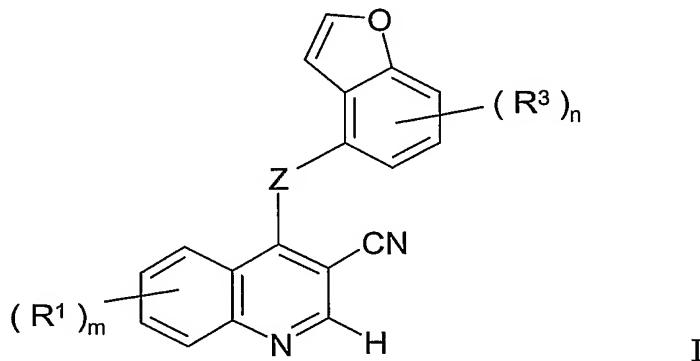
It is stated in International Patent Application WO 98/43960 that a range of 3-cyanoquinoline derivatives are useful in the treatment of cancer. Certain of the compounds are stated to be inhibitors of EGF receptor tyrosine kinase, others are stated to be inhibitors of the mitogen-activated protein kinase (MAPK) pathway and others are stated to be inhibitors of 30 growth factors such as vascular endothelial growth factor (VEGF). There is no disclosure therein of any 4-benzofuranyl amino-3-cyanoquinoline derivatives.

It is stated in International Patent Application WO 00/68201 that a range of 3-cyanoquinoline derivatives are also useful in the treatment of cancer. Certain of the

compounds are stated to be inhibitors of MEK, a MAPK kinase. There is no disclosure therein of any 4-benzofuranyl amino-3-cyanoquinoline derivatives.

It is disclosed in Journal Medicinal Chemistry, 2001, 44, 822-833 and in Journal Medicinal Chemistry, 2001, 44, 3965-3977 that certain 4-anilino-3-cyanoquinoline derivatives 5 are useful for the inhibition of Src-dependent cell proliferation. There is no disclosure therein of any 4-benzofuranyl amino-3-cyanoquinoline derivatives.

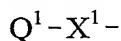
According to one aspect of the invention there is provided a quinoline derivative of the Formula I



10 wherein **Z** is an O, S, SO, SO₂, N(R²) or C(R²)₂ group, wherein each R² group, which may be the same or different, is hydrogen or (1-6C)alkyl;

m is 0, 1, 2, 3 or 4;

each **R**¹ group, which may be the same or different, is selected from halogeno, trifluoromethyl, cyano, isocyano, nitro, hydroxy, mercapto, amino, formyl, carboxy, 15 carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, (3-6C)alkenoylamino, N-(1-6C)alkyl-20 (3-6C)alkenoylamino, (3-6C)alkynoylamino, N-(1-6C)alkyl-(3-6C)alkynoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :



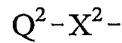
wherein X¹ is a direct bond or is selected from O, S, SO, SO₂, N(R⁴), CO, CH(OR⁴), 25 CON(R⁴), N(R⁴)CO, SO₂N(R⁴), N(R⁴)SO₂, OC(R⁴)₂, SC(R⁴)₂ and N(R⁴)C(R⁴)₂, wherein R⁴ is hydrogen or (1-6C)alkyl, and Q¹ is aryl, aryl-(1-6C)alkyl, (3-7C)cycloalkyl, (3-7C)cycloalkyl-

(1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl, or $(R^1)_m$ is (1-3C)alkylenedioxy,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, S, SO, SO₂,
5 N(R^5), CO, CH(OR^5), CON(R^5), N(R^5)CO, SO₂N(R^5), N(R^5)SO₂, CH=CH and C≡C wherein R^5 is hydrogen or (1-6C)alkyl or, when the inserted group is N(R^5), R^5 may also be (2-6C)alkanoyl,

and wherein any CH₂=CH- or HC≡C- group within a R^1 substituent optionally bears at the terminal CH₂= or HC≡ position a substituent selected from halogeno, carboxy, carbamoyl,

10 (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl and di-[(1-6C)alkyl]amino-(1-6C)alkyl or from a group of the formula :

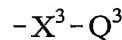


wherein X² is a direct bond or is selected from CO and N(R^6)CO, wherein R^6 is hydrogen or

15 (1-6C)alkyl, and Q² is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any CH₂ or CH₃ group within a R^1 substituent optionally bears on each said CH₂ or CH₃ group one or more halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, cyano, amino, carboxy, carbamoyl, (1-6C)alkoxy, (1-6C)alkylthio,

20 (1-6C)alkylsulphanyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a
25 group of the formula :



wherein X³ is a direct bond or is selected from O, S, SO, SO₂, N(R^7), CO, CH(OR^7),

CON(R^7), N(R^7)CO, SO₂N(R^7), N(R^7)SO₂, C(R^7)₂O, C(R^7)₂S and N(R^7)C(R^7)₂, wherein R^7 is hydrogen or (1-6C)alkyl, and Q³ is aryl, aryl-(1-6C)alkyl, (3-7C)cycloalkyl, (3-7C)cycloalkyl-

30 (1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any aryl, heteroaryl or heterocyclyl group within a substituent on R^1 optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphanyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl- (10) (1-6C)alkanesulphonylamino, or from a group of the formula :

$$-X^4-R^8$$

wherein X^4 is a direct bond or is selected from O and $N(R^9)$, wherein R^9 is hydrogen or (1-6C)alkyl, and R^8 is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl or (1-6C)alkoxycarbonylamino-(1-6C)alkyl, or from a group of the formula :

$$-X^5-Q^4$$

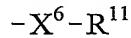
wherein X^5 is a direct bond or is selected from O, $N(R^{10})$ and CO, wherein R^{10} is hydrogen or (1-6C)alkyl, and Q^4 is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl and (1-6C)alkoxy,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo or thioxo substituents;

(25) n is 0, 1, 2 or 3; and

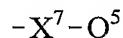
R^3 is halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphanyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, (3-6C)alkenoylamino, N-(1-6C)alkyl-(3-6C)alkenoylamino, N-(1-6C)alkyl-(3-6C)alkynoylamino, (3-6C)alkynoylamino, N-(1-6C)alkyl-(3-6C)alkynoylamino,

N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :



wherein X^6 is a direct bond or is selected from O and $N(R^{12})$, wherein R^{12} is hydrogen or

5 (1-6C)alkyl, and R^{11} is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl or di-[(1-6C)alkyl]amino-(1-6C)alkyl, or from a group of the formula :



wherein X^7 is a direct bond or is selected from O, S, SO, SO_2 , $N(R^{13})$, CO, $CH(OR^{13})$,

10 $CON(R^{13})$, $N(R^{13})CO$, $SO_2N(R^{13})$, $N(R^{13})SO_2$, $C(R^{13})_2O$, $C(R^{13})_2S$ and $N(R^{13})C(R^{13})_2$, wherein R^{13} is hydrogen or (1-6C)alkyl, and Q^5 is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl and (1-6C)alkoxy, and any heterocyclyl group within Q^5 15 optionally bears 1 or 2 oxo or thioxo substituents, or a pharmaceutically-acceptable salt thereof.

In this specification the generic term "alkyl" includes both straight-chain and branched-chain alkyl groups such as propyl, isopropyl and tert-butyl, and also (3-7C)cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and 20 cycloheptyl. However references to individual alkyl groups such as "propyl" are specific for the straight-chain version only, references to individual branched-chain alkyl groups such as "isopropyl" are specific for the branched-chain version only and references to individual cycloalkyl groups such as "cyclopentyl" are specific for that 5-membered ring only. An analogous convention applies to other generic terms, for example (1-6C)alkoxy includes 25 methoxy, ethoxy, cyclopropoxy and cyclopentyloxy, (1-6C)alkylamino includes methylamino, ethylamino, cyclobutylamino and cyclohexylamino, and di-[(1-6C)alkyl]amino includes dimethylamino, diethylamino, N-cyclobutyl-N-methylamino and N-cyclohexyl-N-ethylamino.

It is to be understood that, insofar as certain of the compounds of Formula I defined 30 above may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention includes in its definition any such optically active or racemic form which possesses the above-mentioned activity. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by

synthesis from optically active starting materials or by resolution of a racemic form.

Similarly, the above-mentioned activity may be evaluated using the standard laboratory techniques referred to hereinafter.

Suitable values for the generic radicals referred to above include those set out below.

5 A suitable value for any one of the 'Q' groups (Q¹ to Q⁵) when it is aryl or for the aryl group within a 'Q' group is, for example, phenyl or naphthyl, preferably phenyl.

10 A suitable value for any one of the 'Q' groups (Q¹ or Q³) when it is (3-7C)cycloalkyl or for the (3-7C)cycloalkyl group within a 'Q' group is, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or bicyclo[2.2.1]heptyl and a suitable value for any one of the 'Q' groups (Q¹ or Q³) when it is (3-7C)cycloalkenyl or for the (3-7C)cycloalkenyl group within a 'Q' group is, for example, cyclobutenyl, cyclopentenyl, cyclohexenyl or cycloheptenyl.

15 A suitable value for any one of the 'Q' groups (Q¹ to Q⁵) when it is heteroaryl or for the heteroaryl group within a 'Q' group is, for example, an aromatic 5- or 6-membered monocyclic ring or a 9- or 10-membered bicyclic ring with up to five ring heteroatoms selected from oxygen, nitrogen and sulphur, for example furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazenyl, benzofuranyl, indolyl, benzothienyl, benzoxazolyl, benzimidazolyl, benzothiazolyl, indazolyl, benzofurazanyl, 20 quinolyl, isoquinolyl, quinazolinyl, quinoxalinyl, cinnolinyl or naphthyridinyl.

25 A suitable value for any one of the 'Q' groups (Q¹ to Q⁵) when it is heterocyclyl or for the heterocyclyl group within a 'Q' group is, for example, a non-aromatic saturated or partially saturated 3 to 10 membered monocyclic or bicyclic ring with up to five heteroatoms selected from oxygen, nitrogen and sulphur, for example oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, oxepanyl, tetrahydrothienyl, 1,1-dioxotetrahydrothienyl, tetrahydrothiopyranyl, 1,1-dioxotetrahydrothiopyranyl, azetidinyl, pyrrolinyl, pyrrolidinyl, morpholinyl, tetrahydro-1,4-thiazinyl, 1,1-dioxotetrahydro-1,4-thiazinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl, dihydropyridinyl, tetrahydropyridinyl, dihydropyrimidinyl or tetrahydropyrimidinyl, preferably tetrahydrofuran, tetrahydropyran, pyrrolidinyl, morpholinyl, 1,1-dioxotetrahydro-4H-1,4-thiazinyl, piperidinyl or piperazinyl. A suitable value for such a group which bears 1 or 2 oxo or thioxo substituents is, for example, 2-oxopyrrolidinyl, 2-thioxopyrrolidinyl, 2-oxoimidazolidinyl, 2-thioxoimidazolidinyl, 2-oxopiperidinyl, 2,5-dioxopyrrolidinyl, 2,5-dioxoimidazolidinyl or 2,6-dioxopiperidinyl.

A suitable value for a 'Q' group when it is heteroaryl-(1-6C)alkyl is, for example, heteroarylmethyl, 2-heteroarylethyl and 3-heteroarylpropyl. The invention comprises corresponding suitable values for 'Q' groups when, for example, rather than a heteroaryl-(1-6C)alkyl group, an aryl-(1-6C)alkyl, (3-7C)cycloalkyl-(1-6C)alkyl, 5 (3-7C)cycloalkenyl-(1-6C)alkyl or heterocyclyl-(1-6C)alkyl group is present.

In structural Formula I there is a hydrogen atom at the 2-position on the quinoline ring. It is to be understood thereby that the R¹ substituents may only be located at the 5-, 6-, 7- or 8-positions on the quinoline ring *i.e.* that the 2-position remains unsubstituted. It is further to be understood that the R³ group that may be present on the benzofuranyl group within 10 structural Formula I may be located on either the 5- or 6-membered ring portions thereof, for example at the 2-, 3-, 5-, 6- or 7-positions of the benzofuran-4-yl group. It is further to be understood that, when multiple R³ groups are present, the R³ groups may be the same or different.

Suitable values for any of the 'R' groups (R¹ to R¹³) or for various groups within an R¹ 15 or R³ substituent include :-

for halogeno	fluoro, chloro, bromo and iodo;
for (1-6C)alkyl:	methyl, ethyl, propyl, isopropyl and <u>tert</u> -butyl;
for (2-8C)alkenyl:	vinyl, isopropenyl, allyl and but-2-enyl;
for (2-8C)alkynyl:	ethynyl, 2-propynyl and but-2-ynyl;
20 for (1-6C)alkoxy:	methoxy, ethoxy, propoxy, isopropoxy and butoxy;
for (2-6C)alkenyloxy:	vinyloxy and allyloxy;
for (2-6C)alkynyoxy:	ethynyoxy and 2-propynyoxy;
for (1-6C)alkylthio:	methylthio, ethylthio and propylthio;
for (1-6C)alkylsulphinyl:	methylsulphinyl and ethylsulphinyl;
25 for (1-6C)alkylsulphonyl:	methylsulphonyl and ethylsulphonyl;
for (1-6C)alkylamino:	methylamino, ethylamino, propylamino, isopropylamino and butylamino;
for di-[(1-6C)alkyl]amino:	dimethylamino, diethylamino, <u>N</u> -ethyl- <u>N</u> -methylamino and diisopropylamino;
30 for (1-6C)alkoxycarbonyl:	methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and <u>tert</u> -butoxycarbonyl;
for <u>N</u> -(1-6C)alkylcarbamoyl:	<u>N</u> -methylcarbamoyl, <u>N</u> -ethylcarbamoyl and <u>N</u> -propylcarbamoyl;

for N,N-di-[(1-6C)alkyl]carbamoyl: N,N-dimethylcarbamoyl, N-ethyl-
N-methylcarbamoyl and N,N-diethylcarbamoyl;
for (2-6C)alkanoyl: acetyl and propionyl;
for (2-6C)alkanoyloxy: acetoxy and propionyloxy;
5 for (2-6C)alkanoylamino: acetamido and propionamido;
for N-(1-6C)alkyl-(2-6C)alkanoylamino: N-methylacetamido and N-methylpropionamido;
for N-(1-6C)alkylsulphamoyl: N-methylsulphamoyl and N-ethylsulphamoyl;
for N,N-di-[(1-6C)alkyl]sulphamoyl: N,N-dimethylsulphamoyl;
for (1-6C)alkanesulphonylamino: methanesulphonylamino and ethanesulphonylamino;
10 for N-(1-6C)alkyl-(1-6C)alkanesulphonylamino: N-methylmethanesulphonylamino and
N-methylethanesulphonylamino;
for (3-6C)alkenoylamino: acrylamido, methacrylamido and crotonamido;
for N-(1-6C)alkyl-(3-6C)alkenoylamino: N-methylacrylamido and N-methylcrotonamido;
for (3-6C)alkynoylamino: propiolamido;
15 for N-(1-6C)alkyl-(3-6C)alkynoylamino: N-methylpropiolamido;
for amino-(1-6C)alkyl: aminomethyl, 2-aminoethyl, 1-aminoethyl and
3-aminopropyl;
for (1-6C)alkylamino-(1-6C)alkyl: methylaminomethyl, ethylaminomethyl,
1-methylaminoethyl, 2-methylaminoethyl,
2-ethylaminoethyl and 3-methylaminopropyl;
20 for di-[(1-6C)alkyl]amino-(1-6C)alkyl: dimethylaminomethyl, diethylaminomethyl,
1-dimethylaminoethyl, 2-dimethylaminoethyl and
3-dimethylaminopropyl;
for halogeno-(1-6C)alkyl: chloromethyl, 2-chloroethyl, 1-chloroethyl and
3-chloropropyl;
25 for hydroxy-(1-6C)alkyl: hydroxymethyl, 2-hydroxyethyl, 1-hydroxyethyl and
3-hydroxypropyl;
for (1-6C)alkoxy-(1-6C)alkyl: methoxymethyl, ethoxymethyl, 1-methoxyethyl,
2-methoxyethyl, 2-ethoxyethyl and
3-methoxypropyl;
30 for cyano-(1-6C)alkyl: cyanomethyl, 2-cyanoethyl, 1-cyanoethyl and
3-cyanopropyl;

for (2-6C)alkanoylamino-(1-6C)alkyl: acetamidomethyl, propionamidomethyl and 2-acetamidoethyl; and

for (1-6C)alkoxycarbonylamino-(1-6C)alkyl: methoxycarbonylaminomethyl, ethoxycarbonylaminomethyl, tert-butoxycarbonylaminomethyl and 2-methoxycarbonylaminethyl.

A suitable value for $(R^1)_m$ when it is a (1-3C)alkylenedioxy group is, for example, methylenedioxy or ethylenedioxy and the oxygen atoms thereof occupy adjacent ring positions.

When, as defined hereinbefore, an R^1 group forms a group of the formula Q^1-X^1- and, for example, X^1 is a $OC(R^4)_2$ linking group, it is the carbon atom, not the oxygen atom, of the $OC(R^4)_2$ linking group which is attached to the quinoline ring and the oxygen atom is attached to the Q^1 group. Similarly, when, for example a CH_3 group within a R^1 substituent bears a group of the formula $-X^3-Q^3$ and, for example, X^3 is a $C(R^7)_2O$ linking group, it is the carbon atom, not the oxygen atom, of the $C(R^7)_2O$ linking group which is attached to the CH_3 group and the oxygen atom is linked to the Q^3 group. A similar convention applies to the attachment of the groups of the formulae Q^2-X^2- and $-X^7-Q^5$.

As defined hereinbefore, adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent may be optionally separated by the insertion into the chain of a group such as O , $CON(R^5)$ or $C\equiv C$. For example, insertion of a $C\equiv C$ group into the ethylene chain within a 2-morpholinoethoxy group gives rise to a 4-morpholinobut-2-ynoxy group and, for example, insertion of a $CONH$ group into the ethylene chain within a 3-methoxypropoxy group gives rise to, for example, a 2-(2-methoxyacetamido)ethoxy group.

When, as defined hereinbefore, any $CH_2=CH-$ or $HC\equiv C-$ group within a R^1 substituent optionally bears at the terminal $CH_2=$ or $HC\equiv$ position a substituent such as a group of the formula Q^2-X^2- wherein X^2 is, for example, $NHCO$ and Q^2 is a heterocycl-(1-6C)alkyl group, suitable R^1 substituents so formed include, for example, N-[heterocycl-(1-6C)alkyl]carbamoylvinyl groups such as N-(2-pyrrolidin-1-ylethyl)carbamoylvinyl or N-[heterocycl-(1-6C)alkyl]carbamoylethynyl groups such as N-(2-pyrrolidin-1-ylethyl)carbamoylethynyl.

When, as defined hereinbefore, any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more halogeno or (1-6C)alkyl

substituents, there are suitably 1 or 2 halogeno or (1-6C)alkyl substituents present on each said CH₂ group and there are suitably 1, 2 or 3 such substituents present on each said CH₃ group.

When, as defined hereinbefore, any CH₂ or CH₃ group within a R¹ substituent optionally bears on each said CH₂ or CH₃ group a substituent as defined hereinbefore, suitable 5 R¹ substituents so formed include, for example, hydroxy-substituted heterocycl-(1-6C)alkoxy groups such as 2-hydroxy-3-piperidinopropoxy and 2-hydroxy-3-morpholinopropoxy, hydroxy-substituted amino-(2-6C)alkoxy groups such as 3-amino-2-hydroxypropoxy, hydroxy-substituted (1-6C)alkylamino-(2-6C)alkoxy groups such as 2-hydroxy-3-methylaminopropoxy, hydroxy-substituted di-[(1-6C)alkyl]amino-(2-6C)alkoxy 10 groups such as 3-dimethylamino-2-hydroxypropoxy, hydroxy-substituted heterocycl-(1-6C)alkylamino groups such as 2-hydroxy-3-piperidinopropylamino and 2-hydroxy-3-morpholinopropylamino, hydroxy-substituted amino-(2-6C)alkylamino groups such as 3-amino-2-hydroxypropylamino, hydroxy-substituted (1-6C)alkylamino-(2-6C)alkylamino groups such as 2-hydroxy-3-methylaminopropylamino, hydroxy-substituted 15 di-[(1-6C)alkyl]amino-(2-6C)alkylamino groups such as 3-dimethylamino-2-hydroxypropylamino, hydroxy-substituted (1-6C)alkoxy groups such as 2-hydroxyethoxy, (1-6C)alkoxy-substituted (1-6C)alkoxy groups such as 2-methoxyethoxy and 3-ethoxypropoxy, (1-6C)alkylsulphonyl-substituted (1-6C)alkoxy groups such as 2-methylsulphonylethoxy and heterocycl-substituted (1-6C)alkylamino-(1-6C)alkyl groups 20 such as 2-morpholinoethylaminomethyl, 2-piperazin-1-ylethylaminomethyl and 3-morpholinopropylaminomethyl.

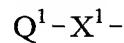
A suitable pharmaceutically-acceptable salt of a compound of the Formula I is, for example, an acid-addition salt of a compound of the Formula I, for example an acid-addition salt with an inorganic or organic acid such as hydrochloric, hydrobromic, sulphuric, 25 trifluoroacetic, citric or maleic acid; or, for example, a salt of a compound of the Formula I which is sufficiently acidic, for example an alkali or alkaline earth metal salt such as a calcium or magnesium salt, or an ammonium salt, or a salt with an organic base such as methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

30 Particular novel compounds of the invention include, for example, quinoline derivatives of the Formula I, or pharmaceutically-acceptable salts thereof, wherein, unless otherwise stated, each of Z, m, R¹, n and R³ has any of the meanings defined hereinbefore or in paragraphs (a) to (q) hereinafter :-

- (a) Z is O, S, SO, SO₂, CH₂ or NH;
- (b) Z is O;
- (c) Z is NH;
- (d) m is 1 or 2, and each R¹ group, which may be the same or different, is selected from

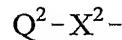
5 halogeno, trifluoromethyl, hydroxy, amino, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, (3-6C)alkenoylamino, N-(1-6C)alkyl-(3-6C)alkenoylamino, (3-6C)alkynoylamino and N-(1-6C)alkyl-

10 (3-6C)alkynoylamino, or from a group of the formula :

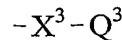


wherein X¹ is a direct bond or is selected from O, N(R⁴), CON(R⁴), N(R⁴)CO and OC(R⁴)₂ wherein R⁴ is hydrogen or (1-6C)alkyl, and Q¹ is aryl, aryl-(1-6C)alkyl, cycloalkyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl, and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R¹ substituent are optionally separated by the insertion into the chain of a group selected from O, N(R⁵), CON(R⁵), N(R⁵)CO, CH=CH and C≡C wherein R⁵ is hydrogen or (1-6C)alkyl, or, when the inserted group is N(R⁵), R⁵ may also be (2-6C)alkanoyl,

15 and wherein any CH₂=CH- or HC≡C- group within a R¹ substituent optionally bears at the terminal CH₂= or HC≡ position a substituent selected from carbamoyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl and di-[(1-6C)alkyl]amino-(1-6C)alkyl or from a group of the formula :



20 25 wherein X² is a direct bond or is CO or N(R⁶)CO, wherein R⁶ is hydrogen or (1-6C)alkyl, and Q² is heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl, and wherein any CH₂ or CH₃ group within a R¹ substituent optionally bears on each said CH₂ or CH₃ group one or more halogeno groups or a substituent selected from hydroxy, amino, (1-6C)alkoxy, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (2-6C)alkanoyloxy, (2-6C)alkanoylamino and N-(1-6C)alkyl-(2-6C)alkanoylamino, or from a group of the formula :



wherein X^3 is a direct bond or is selected from O, N(R⁶), CON(R⁷), N(R⁷)CO and C(R⁷)₂O, wherein R⁷ is hydrogen or (1-6C)alkyl, and Q³ is heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any aryl, heteroaryl or heterocyclyl group within a substituent on R¹

5 optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, hydroxy, amino, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (1-6C)alkylsulphonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl and (2-6C)alkanoyl, or optionally bears 1 substituent selected from a group of the formula :

10 $-X^4-R^8$

wherein X⁴ is a direct bond or is selected from O and N(R⁹), wherein R⁹ is hydrogen or (1-6C)alkyl, and R⁸ is hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl or (1-6C)alkoxycarbonylamino-(1-6C)alkyl, and from a 15 group of the formula :

$-X^5-Q^4$

wherein X⁵ is a direct bond or is selected from O, N(R¹⁰) and CO, wherein R¹⁰ is hydrogen or (1-6C)alkyl, and Q⁴ is heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, (1-6C)alkyl and 20 (1-6C)alkoxy,

and wherein any heterocyclyl group within a substituent on R¹ optionally bears 1 or 2 oxo substituents;

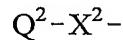
(e) m is 1 or 2, and each R¹ group, which may be the same or different, is selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, carbamoyl, methyl, ethyl, propyl, butyl, vinyl, 25 allyl, but-3-enyl, pent-4-enyl, hex-5-enyl, ethynyl, 2-propynyl, but-3-ynyl, pent-4-ynyl, hex-5-ynyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, allyloxy, but-3-enoxy, pent-4-enoxy, hex-5-enoxy, ethynyoxy, 2-propynyoxy, but-3-ynyloxy, pent-4-ynyloxy, hex-5-ynyloxy, methylamino, ethylamino, propylamino, dimethylamino, diethylamino, dipropylamino, N-methylcarbamoyl, N,N-dimethylcarbamoyl, acetamido, propionamido, 30 acrylamido and propiolamido, or from a group of the formula :

Q^1-X^1-

wherein X¹ is a direct bond or is selected from O, NH, CONH, NHCO and OCH₂ and Q¹ is phenyl, benzyl, cyclopropylmethyl, 2-thienyl, 1-imidazolyl, 1,2,3-triazol-1-yl,

1,2,4-triazol-1-yl, 2-, 3- or 4-pyridyl, 2-imidazol-1-ylethyl, 3-imidazol-1-ylpropyl,
 2-(1,2,3-triazolyl)ethyl, 3-(1,2,3-triazolyl)propyl, 2-(1,2,4-triazolyl)ethyl,
 3-(1,2,4-triazolyl)propyl, 2-, 3- or 4-pyridylmethyl, 2-(2-, 3- or 4-pyridyl)ethyl,
 3-(2-, 3- or 4-pyridyl)propyl, tetrahydrofuran-3-yl, 3- or 4-tetrahydropyranyl,
 5 1-, 2- or 3-pyrrolidinyl, morpholino, 1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl, piperidino,
 piperidin-3-yl, piperidin-4-yl, 1-, 3- or 4-homopiperidinyl, piperazin-1-yl, homopiperazin-1-yl,
 1-, 2- or 3-pyrrolidinylmethyl, morpholinomethyl, piperidinomethyl,
 3- or 4-piperidinylmethyl, 1-, 3- or 4-homopiperidinylmethyl, 2-pyrrolidin-1-ylethyl,
 3-pyrrolidin-2-ylpropyl, pyrrolidin-2-ylmethyl, 2-pyrrolidin-2-ylethyl, 3-pyrrolidin-1-ylpropyl,
 10 4-pyrrolidin-1-ylbutyl, 2-morpholinoethyl, 3-morpholinopropyl, 4-morpholinobutyl,
 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethyl, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-
 4-yl)propyl, 2-piperidinoethyl, 3-piperidinopropyl, 4-piperidinobutyl, 2-piperidin-3-ylethyl,
 3-piperidin-3-ylpropyl, 2-piperidin-4-ylethyl, 3-piperidin-4-ylpropyl,
 2-homopiperidin-1-ylethyl, 3-homopiperidin-1-ylpropyl, 2-piperazin-1-ylethyl,
 15 3-piperazin-1-ylpropyl, 4-piperazin-1-ylbutyl, 2-homopiperazin-1-ylethyl or
 3-homopiperazin-1-ylpropyl,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R¹ substituent
 are optionally separated by the insertion into the chain of a group selected from O, NH,
 N(Me), CONH, NHCO, CH=CH and C≡C,
 20 and wherein any CH₂=CH- or HC≡C- group within a R¹ substituent optionally bears at
 the terminal CH₂= or HC≡ position a substituent selected from carbamoyl,
N-methylcarbamoyl, N-ethylcarbamoyl, N-propylcarbamoyl, N,N-dimethylcarbamoyl,
 aminomethyl, 2-aminoethyl, 3-aminopropyl, 4-aminobutyl, methylaminomethyl,
 2-methylaminoethyl, 3-methylaminopropyl, 4-methylaminobutyl, dimethylaminomethyl,
 25 2-dimethylaminoethyl, 3-dimethylaminopropyl or 4-dimethylaminobutyl, or from a group of
 the formula :



wherein X² is a direct bond or is CO, NHCO or N(Me)CO and Q² is pyridyl, pyridylmethyl,
 2-pyridylethyl, pyrrolidin-1-yl, pyrrolidin-2-yl, morpholino, piperidino, piperidin-3-yl,
 30 piperidin-4-yl, piperazin-1-yl, pyrrolidin-1-ylmethyl, 2-pyrrolidin-1-ylethyl,
 3-pyrrolidin-1-ylpropyl, 4-pyrrolidin-1-ylbutyl, pyrrolidin-2-ylmethyl, 2-pyrrolidin-2-ylethyl,
 3-pyrrolidin-2-ylpropyl, morpholinomethyl, 2-morpholinoethyl, 3-morpholinopropyl,

4-morpholinobutyl, piperidinomethyl, 2-piperidinoethyl, 3-piperidinopropyl,
 4-piperidinobutyl, piperidin-3-ylmethyl, 2-piperidin-3-ylethyl, piperidin-4-ylmethyl,
 2-piperidin-4-ylethyl, piperazin-1-ylmethyl, 2-piperazin-1-ylethyl, 3-piperazin-1-ylpropyl or
 4-piperazin-1-ylbutyl,

5 and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each
 said CH_2 or CH_3 group one or more fluoro or chloro groups or a substituent selected from
 hydroxy, amino, methoxy, methylsulphonyl, methylamino, dimethylamino, diisopropylamino,
N-ethyl-N-methylamino, N-isopropyl-N-methylamino, N-methyl-N-propylamino, acetoxy,
 acetamido and N-methylacetamido or from a group of the formula :

10 $-\text{X}^3-\text{Q}^3$

wherein X^3 is a direct bond or is selected from O, NH, CONH, NHCO and CH_2O and Q^3 is
 pyridyl, pyridylmethyl, pyrrolidin-1-yl, pyrrolidin-2-yl, morpholino, piperidino, piperidin-3-yl,
 piperidin-4-yl, piperazin-1-yl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, pyrrolidin-
 2-ylmethyl, 2-pyrrolidin-2-ylethyl, 3-pyrrolidin-2-ylpropyl, 2-morpholinoethyl,
 15 3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, piperidin-3-ylmethyl, 2-piperidin-
 3-ylethyl, piperidin-4-ylmethyl, 2-piperidin-4-ylethyl, 2-piperazin-1-ylethyl or 3-piperazin-
 1-ylpropyl,

20 and wherein any aryl, heteroaryl or heterocyclyl group within a substituent on R^1
 optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from
 fluoro, chloro, trifluoromethyl, hydroxy, amino, carbamoyl, methyl, ethyl, allyl, 2-propynyl,
 methoxy, methylsulphonyl, N-methylcarbamoyl, N,N-dimethylcarbamoyl and acetyl,
 or optionally bears 1 substituent selected from a group of the formula :

25 $-\text{X}^4-\text{R}^8$

wherein X^4 is a direct bond or is selected from O and NH and R^8 is 2-hydroxyethyl,
 3-hydroxypropyl, 2-methoxyethyl, 3-methoxypropyl, cyanomethyl, aminomethyl,
 2-aminoethyl, 3-aminopropyl, methylaminomethyl, 2-methylaminoethyl,
 3-methylaminopropyl, 2-ethylaminoethyl, 3-ethylaminopropyl, dimethylaminomethyl,
 2-dimethylaminoethyl, 3-dimethylaminopropyl, acetamidomethyl,
 methoxycarbonylaminomethyl, ethoxycarbonylaminomethyl or
 30 tert-butoxycarbonylaminomethyl, and from a group of the formula :

$-\text{X}^5-\text{Q}^4$

wherein X^5 is a direct bond or is selected from O, NH and CO and Q^4 is
 pyrrolidin-1-ylmethyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, morpholinomethyl,

2-morpholinoethyl, 3-morpholinopropyl, piperidinomethyl, 2-piperidinoethyl, 3-piperidinopropyl, piperazin-1-ylmethyl, 2-piperazin-1-ylethyl or 3-piperazin-1-ylpropyl, each of which optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, methyl and methoxy,

5 and wherein any heterocyclyl group within a substituent on R¹ optionally bears 1 or 2 oxo substituents; and

(f) m is 1 and the R¹ group is located at the 5-, 6- or 7-position or m is 2 and each R¹ group, which may be the same or different, is located at the 5- and 7-positions or at the 6- and 7-positions and R¹ is selected from hydroxy, amino, methyl, ethyl, propyl, butyl, vinyl, 10 ethynyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, pentyloxy, but-3-enyloxy, pent-4-enyloxy, hex-5-enyloxy, but-3-nyloxy, pent-4-nyloxy, hex-5-nyloxy, methylamino, ethylamino, dimethylamino, diethylamino, acetamido, propionamido, cyclopentyloxy, cyclohexyloxy, phenoxy, benzyloxy, tetrahydrofuran-3-yloxy, tetrahydropyran-3-yloxy, tetrahydropyran-4-yloxy, cyclopropylmethoxy, 2-imidazol-1-ylethoxy, 15 3-imidazol-1-ylpropoxy, 2-(1,2,3-triazol-1-yl)ethoxy, 3-(1,2,3-triazol-1-yl)propoxy, 2-(1,2,4-triazol-1-yl)ethoxy, 3-(1,2,4-triazol-1-yl)propoxy, pyrid-2-ylmethoxy, pyrid-3-ylmethoxy, pyrid-4-ylmethoxy, 2-pyrid-2-ylethoxy, 2-pyrid-3-ylethoxy, 2-pyrid-4-ylethoxy, 3-pyrid-2-ylpropoxy, 3-pyrid-3-ylpropoxy, 3-pyrid-4-ylpropoxy, 20 pyrrolidin-1-yl, morpholino, piperidino, piperazin-1-yl, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 4-pyrrolidin-1-ylbutoxy, pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 4-morpholinobutoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy, piperidin-3-yloxy, 25 piperidin-4-yloxy, piperidin-3-ylmethoxy, piperidin-4-ylmethoxy, 2-piperidin-3-ylethoxy, 3-piperidin-3-ylpropoxy, 2-piperidin-4-ylethoxy, 3-piperidin-4-ylpropoxy, 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 4-piperazin-1-ylbutoxy, 2-homopiperazin-1-ylethoxy, 3-homopiperazin-1-ylpropoxy, 2-pyrrolidin-1-ylethylamino, 3-pyrrolidin-1-ylpropylamino, 30 4-pyrrolidin-1-ylbutylamino, pyrrolidin-3-ylamino, pyrrolidin-2-ylmethylethylamino, 2-pyrrolidin-2-ylethylamino, 3-pyrrolidin-2-ylpropylamino, 2-morpholinoethylamino, 3-morpholinopropylamino, 4-morpholinobutylamino, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethylamino, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propylamino,

2-piperidinoethylamino, 3-piperidinopropylamino, 4-piperidinobutylamino,
 piperidin-3-ylamino, piperidin-4-ylamino, piperidin-3-ylmethylamino,
 2-piperidin-3-ylethylamino, piperidin-4-ylmethylamino, 2-piperidin-4-ylethylamino,
 2-homopiperidin-1-ylethylamino, 3-homopiperidin-1-ylpropylamino,
 5 2-piperazin-1-ylethylamino, 3-piperazin-1-ylpropylamino, 4-piperazin-1-ylbutylamino,
 2-homopiperazin-1-ylethylamino or 3-homopiperazin-1-ylpropylamino,
 and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R¹ substituent
 are optionally separated by the insertion into the chain of a group selected from O, NH,
 N(Me), CH=CH and C≡C,
 10 and when R¹ is a vinyl or ethynyl group, the R¹ substituent optionally bears at the
 terminal CH₂= or HC≡ position a substituent selected from
N-(2-dimethylaminoethyl)carbamoyl, N-(3-dimethylaminopropyl)carbamoyl,
 methylaminomethyl, 2-methylaminoethyl, 3-methylaminopropyl, 4-methylaminobutyl,
 dimethylaminomethyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl and
 15 4-dimethylaminobutyl, or from a group of the formula :

$$Q^2-X^2-$$

 wherein X² is a direct bond or is NHCO or N(Me)CO and Q² is imidazolylmethyl,
 2-imidazolylethyl, 3-imidazolylpropyl, pyridylmethyl, 2-pyridylethyl, 3-pyridylpropyl,
 pyrrolidin-1-ylmethyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, 4-pyrrolidin-1-ylbutyl,
 20 pyrrolidin-2-ylmethyl, 2-pyrrolidin-2-ylethyl, 3-pyrrolidin-2-ylpropyl, morpholinomethyl,
 2-morpholinoethyl, 3-morpholinopropyl, 4-morpholinobutyl, piperidinomethyl,
 2-piperidinoethyl, 3-piperidinopropyl, 4-piperidinobutyl, piperidin-3-ylmethyl,
 2-piperidin-3-ylethyl, piperidin-4-ylmethyl, 2-piperidin-4-ylethyl, piperazin-1-ylmethyl,
 2-piperazin-1-ylethyl, 3-piperazin-1-ylpropyl or 4-piperazin-1-ylbutyl,
 25 and wherein any CH₂ or CH₃ group within a R¹ substituent optionally bears on each
 said CH₂ or CH₃ group one or more fluoro or chloro groups or a substituent selected from
 hydroxy, amino, methoxy, methylsulphonyl, methylamino, dimethylamino, diisopropylamino,
N-ethyl-N-methylamino, N-isopropyl-N-methylamino, N-methyl-N-propylamino, acetoxy,
 acetamido and N-methylacetamido,
 30 and wherein any phenyl, imidazolyl, triazolyl, pyridyl or heterocyclyl group within a
 substituent on R¹ optionally bears 1 or 2 substituents, which may be the same or different,
 selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, carbamoyl, methyl, ethyl,

N-methylcarbamoyl, N,N-dimethylcarbamoyl and methoxy, and a pyrrolidin-2-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl or homopiperazin-1-yl group within a R¹ substituent is optionally N-substituted with allyl, 2-propynyl, methylsulphonyl, acetyl, 2-methoxyethyl, 3-methoxypropyl, cyanomethyl, 2-aminoethyl, 3-aminopropyl, 5 2-methylaminoethyl, 3-methylaminopropyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, 2-morpholinoethyl, 3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, 2-piperazin-1-ylethyl or 3-piperazin-1-ylpropyl, the last 8 of which substituents each optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, methyl and methoxy,

10 and wherein any heterocyclyl group within a substituent on R¹ optionally bears 1 or 2 oxo substituents.

(g) m is 1 and the R¹ group is located at the 6- or 7-position and is selected from hydroxy, amino, methyl, ethyl, propyl, butyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, methylamino, ethylamino, dimethylamino, diethylamino, acetamido, propionamido, 15 benzyloxy, 2-imidazol-1-ylethoxy, 2-(1,2,3-triazol-1-yl)ethoxy, 2-(1,2,4-triazol-1-yl)ethoxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 4-pyrrolidin-1-ylbutoxy, pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 4-morpholinobutoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-20 4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy, piperidin-3-yloxy, piperidin-4-yloxy, piperidin-3-ylmethoxy, 2-piperidin-3-ylethoxy, piperidin-4-ylmethoxy, 2-piperidin-4-ylethoxy, 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-homopiperazin-1-ylethoxy or 3-homopiperazin-1-ylpropoxy,

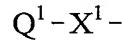
25 and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R¹ substituent are optionally separated by the insertion into the chain of a group selected from O, NH, CH=CH and C≡C,

and wherein any CH₂ or CH₃ group within a R¹ substituent optionally bears on each said CH₂ or CH₃ group one or more chloro groups or a substituent selected from hydroxy, 30 amino, methoxy, methylsulphonyl, methylamino, dimethylamino, diisopropylamino, N-ethyl-N-methylamino, N-isopropyl-N-methylamino and acetoxy,

and wherein any phenyl or heterocyclyl group within a substituent on R¹ optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, methyl, ethyl and methoxy,

and wherein any heterocyclyl group within a substituent on R¹ optionally bears 1 or 2 oxo substituents;

- (h) n is 0;
- (i) n is 1 or 2 and the R³ groups, which may be the same or different, are located at the 3-, 5- and/or 6-positions of the benzofuran-4-yl group and are selected from halogeno, trifluoromethyl, cyano, hydroxy, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl and (1-6C)alkoxy;
- (j) n is 1 or 2 and the R³ groups, which may be the same or different, are located at the 3-, 5- and/or 6-positions of the benzofuran-4-yl group and are selected from fluoro, chloro, bromo, iodo, trifluoromethyl, cyano, hydroxy, methyl, ethyl, vinyl, allyl, isopropenyl, ethynyl, 1-propynyl, 2-propynyl, methoxy and ethoxy;
- (k) n is 1 and the R³ group is located at the 5- or 6-position of the benzofuran-4-yl group, especially the 6-position, and is selected from chloro, bromo, trifluoromethyl, cyano, hydroxy, methyl, ethyl, methoxy and ethoxy;
- (l) m is 1 or 2, and each R¹ group, which may be the same or different, is selected from halogeno, trifluoromethyl, hydroxy, amino, carbamoyl, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoylamino and N-(1-6C)alkyl-(2-6C)alkanoylamino, or from a group of the formula :

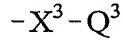


wherein X¹ is selected from O, N(R⁴), CON(R⁴), N(R⁴)CO and OC(R⁴)₂ wherein R⁴ is hydrogen or (1-6C)alkyl, and Q¹ is aryl, aryl-(1-6C)alkyl, cycloalkyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl, or X¹ is a direct bond and Q¹ is aryl-(1-6C)alkyl, cycloalkyl-(1-6C)alkyl, heteroaryl-(1-6C)alkyl or heterocyclyl-(1-6C)alkyl,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R¹ substituent are optionally separated by the insertion into the chain of a group selected from O, N(R⁵), CON(R⁵), N(R⁵)CO, CH=CH and C≡C wherein R⁵ is hydrogen or (1-6C)alkyl, or, when the inserted group is N(R⁵), R⁵ may also be (2-6C)alkanoyl,

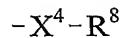
and wherein any CH₂ or CH₃ group within a R¹ substituent optionally bears on each said CH₂ or CH₃ group one or more halogeno groups or a substituent selected from hydroxy,

amino, (1-6C)alkoxy, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (2-6C)alkanoyloxy, (2-6C)alkanoylamino and N-(1-6C)alkyl-(2-6C)alkanoylamino, or from a group of the formula :

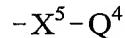


5 wherein X^3 is a direct bond or is selected from O, $N(R^6)$, $CON(R^7)$, $N(R^7)CO$ and $C(R^7)_2O$, wherein R^7 is hydrogen or (1-6C)alkyl, and Q^3 is heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any aryl, heteroaryl or heterocyclyl group within a substituent on R^1 optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from 10 halogeno, trifluoromethyl, hydroxy, amino, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (1-6C)alkylsulphonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl and (2-6C)alkanoyl, or optionally bears 1 substituent selected from a group of the formula :



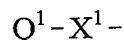
15 wherein X^4 is a direct bond or is selected from O and $N(R^9)$, wherein R^9 is hydrogen or (1-6C)alkyl, and R^8 is hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl or (1-6C)alkoxycarbonylamino-(1-6C)alkyl, and from a group of the formula :



20 wherein X^5 is a direct bond or is selected from O, $N(R^{10})$ and CO, wherein R^{10} is hydrogen or (1-6C)alkyl, and Q^4 is heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, (1-6C)alkyl and (1-6C)alkoxy,

25 and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo substituents;

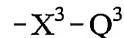
(m) m is 1 or 2, and each R^1 group, which may be the same or different, is selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, carbamoyl, methyl, ethyl, propyl, butyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, methylamino, ethylamino, propylamino, 30 dimethylamino, diethylamino, dipropylamino, N-methylcarbamoyl, N,N-dimethylcarbamoyl, acetamido, propionamido, acrylamido and propiolamido, or from a group of the formula :



wherein X^1 is selected from O, NH, CONH, NHCO and OCH_2 and Q^1 is phenyl, benzyl, cyclopropylmethyl, 2-thienyl, 1-imidazolyl, 1,2,3-triazol-1-yl, 1,2,4-triazol-1-yl, 2-, 3- or 4-pyridyl, 2-imidazol-1-ylethyl, 3-imidazol-1-ylpropyl, 2-(1,2,3-triazolyl)ethyl, 3-(1,2,3-triazolyl)propyl, 2-(1,2,4-triazolyl)ethyl, 3-(1,2,4-triazolyl)propyl, 2-, 3- or 4-pyridylmethyl, 2-(2-, 3- or 4-pyridyl)ethyl, 3-(2-, 3- or 4-pyridyl)propyl, tetrahydrofuran-3-yl, 3- or 4-tetrahydropyran, 1-, 2- or 3-pyrrolidinyl, morpholino, 1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl, piperidino, piperidin-3-yl, piperidin-4-yl, 1-, 3- or 4-homopiperidinyl, piperazin-1-yl, homopiperazin-1-yl, 1-, 2- or 3-pyrrolidinylmethyl, morpholinomethyl, piperidinomethyl, 3- or 4-piperidinylmethyl, 1-, 3- or 4-homopiperidinylmethyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-2-ylpropyl, pyrrolidin-2-ylmethyl, 2-pyrrolidin-2-ylethyl, 3-pyrrolidin-1-ylpropyl, 4-pyrrolidin-1-ylbutyl, 2-morpholinoethyl, 3-morpholinopropyl, 4-morpholinobutyl, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethyl, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propyl, 2-piperidinoethyl, 3-piperidinopropyl, 4-piperidinobutyl, 2-piperidin-3-ylethyl, 15 3-piperidin-3-ylpropyl, 2-piperidin-4-ylethyl, 3-piperidin-4-ylpropyl, 2-homopiperidin-1-ylethyl, 3-homopiperidin-1-ylpropyl, 2-(1,2,3,6-tetrahydropyridin-1-yl)ethyl, 3-(1,2,3,6-tetrahydropyridin-1-yl)propyl, 4-(1,2,3,6-tetrahydropyridin-1-yl)butyl, 2-piperazin-1-ylethyl, 3-piperazin-1-ylpropyl, 4-piperazin-1-ylbutyl, 2-homopiperazin-1-ylethyl or 3-homopiperazin-1-ylpropyl, 20 or wherein X^1 is a direct bond and Q^1 is benzyl, cyclopropylmethyl, 2-imidazol-1-ylethyl, 3-imidazol-1-ylpropyl, 2-(1,2,3-triazolyl)ethyl, 3-(1,2,3-triazolyl)propyl, 2-(1,2,4-triazolyl)ethyl, 3-(1,2,4-triazolyl)propyl, 2-, 3- or 4-pyridylmethyl, 2-(2-, 3- or 4-pyridyl)ethyl, 3-(2-, 3- or 4-pyridyl)propyl, 1-, 2- or 3-pyrrolidinylmethyl, morpholinomethyl, piperidinomethyl, 3- or 4-piperidinylmethyl, 1-, 3- or 4-homopiperidinylmethyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-2-ylpropyl, pyrrolidin-2-ylmethyl, 2-pyrrolidin-2-ylethyl, 3-pyrrolidin-1-ylpropyl, 4-pyrrolidin-1-ylbutyl, 2-morpholinoethyl, 3-morpholinopropyl, 4-morpholinobutyl, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethyl, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propyl, 2-piperidinoethyl, 3-piperidinopropyl, 4-piperidinobutyl, 2-piperidin-3-ylethyl, 25 3-piperidin-3-ylpropyl, 2-piperidin-4-ylethyl, 3-piperidin-4-ylpropyl, 2-homopiperidin-1-ylethyl, 3-homopiperidin-1-ylpropyl, 2-piperazin-1-ylethyl, 3-piperazin-1-ylpropyl, 4-piperazin-1-ylbutyl, 2-homopiperazin-1-ylethyl or 3-homopiperazin-1-ylpropyl, 30 3-piperidin-3-ylpropyl, 2-piperidin-4-ylethyl, 3-piperidin-4-ylpropyl, 2-homopiperidin-1-ylethyl, 3-homopiperidin-1-ylpropyl, 2-piperazin-1-ylethyl, 3-piperazin-1-ylpropyl, 4-piperazin-1-ylbutyl, 2-homopiperazin-1-ylethyl or 3-homopiperazin-1-ylpropyl,

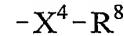
and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R¹ substituent are optionally separated by the insertion into the chain of a group selected from O, NH, N(Me), CONH, NHCO, CH=CH and C≡C,

and wherein any CH₂ or CH₃ group within a R¹ substituent optionally bears on each 5 said CH₂ or CH₃ group one or more fluoro or chloro groups or a substituent selected from hydroxy, amino, methoxy, methylsulphonyl, methylamino, dimethylamino, diisopropylamino, N-ethyl-N-methylamino, N-isopropyl-N-methylamino, N-methyl-N-propylamino, acetoxy, acetamido and N-methylacetamido or from a group of the formula :



10 wherein X³ is a direct bond or is selected from O, NH, CONH, NHCO and CH₂O and Q³ is pyridyl, pyridylmethyl, pyrrolidin-1-yl, pyrrolidin-2-yl, morpholino, piperidino, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, pyrrolidin-2-ylmethyl, 2-pyrrolidin-2-ylethyl, 3-pyrrolidin-2-ylpropyl, 2-morpholinoethyl, 3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, piperidin-3-ylmethyl, 2-piperidin-13-ylethyl, piperidin-4-ylmethyl, 2-piperidin-4-ylethyl, 2-piperazin-1-ylethyl or 3-piperazin-1-ylpropyl,

and wherein any aryl, heteroaryl or heterocyclyl group within a substituent on R¹ 20 optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, carbamoyl, methyl, ethyl, allyl, 2-propynyl, methoxy, methylsulphonyl, N-methylcarbamoyl, N,N-dimethylcarbamoyl and acetyl, or optionally bears 1 substituent selected from a group of the formula :



wherein X⁴ is a direct bond or is selected from O and NH and R⁸ is 2-hydroxyethyl, 3-hydroxypropyl, 2-methoxyethyl, 3-methoxypropyl, cyanomethyl, aminomethyl, 25 2-aminoethyl, 3-aminopropyl, methylaminomethyl, 2-methylaminooethyl, 3-methylaminopropyl, 2-ethylaminooethyl, 3-ethylaminopropyl, dimethylaminomethyl, 2-dimethylaminooethyl, 3-dimethylaminopropyl, acetamidomethyl, methoxycarbonylaminomethyl, ethoxycarbonylaminomethyl or tert-butoxycarbonylaminomethyl, and from a group of the formula :



30 wherein X⁵ is a direct bond or is selected from O, NH and CO and Q⁴ is pyrrolidin-1-ylmethyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, morpholinomethyl, 2-morpholinoethyl, 3-morpholinopropyl, piperidinomethyl, 2-piperidinoethyl,

3-piperidinopropyl, piperazin-1-ylmethyl, 2-piperazin-1-ylethyl or 3-piperazin-1-ylpropyl, each of which optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, methyl and methoxy,

and wherein any heterocyclyl group within a substituent on R¹ optionally bears 1 or 2

5 oxo substituents;

(n) m is 1 and the R¹ group is located at the 5-, 6- or 7-position or m is 2 and each R¹ group, which may be the same or different, is located at the 5- and 7-positions or at the 6- and 7-positions and R¹ is selected from hydroxy, amino, methyl, ethyl, propyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, pentyloxy, methylamino, ethylamino, dimethylamino, 10 diethylamino, acetamido, propionamido, cyclopentyloxy, cyclohexyloxy, phenoxy, benzyloxy, tetrahydrofuran-3-yloxy, tetrahydropyran-3-yloxy, tetrahydropyran-4-yloxy, cyclopropylmethoxy, 2-imidazol-1-ylethoxy, 3-imidazol-1-ylpropoxy, 2-(1,2,3-triazol-1-yl)ethoxy, 3-(1,2,3-triazol-1-yl)propoxy, 2-(1,2,4-triazol-1-yl)ethoxy, 3-(1,2,4-triazol-1-yl)propoxy, pyrid-2-ylmethoxy, pyrid-3-ylmethoxy, pyrid-4-ylmethoxy, 15 2-pyrid-2-ylethoxy, 2-pyrid-3-ylethoxy, 2-pyrid-4-ylethoxy, 3-pyrid-2-ylpropoxy, 3-pyrid-3-ylpropoxy, 3-pyrid-4-ylpropoxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 4-pyrrolidin-1-ylbutoxy, pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 4-morpholinobutoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro- 20 4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy, piperidin-3-yloxy, piperidin-4-yloxy, piperidin-3-ylmethoxy, piperidin-4-ylmethoxy, 2-piperidin-3-ylethoxy, 3-piperidin-3-ylpropoxy, 2-piperidin-4-ylethoxy, 3-piperidin-4-ylpropoxy, 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, 2-(1,2,3,6-tetrahydropyridin-1-yl)ethoxy, 3-(1,2,3,6-tetrahydropyridin-1-yl)propoxy, 25 4-(1,2,3,6-tetrahydropyridin-1-yl)butoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 4-piperazin-1-ylbutoxy, 2-homopiperazin-1-ylethoxy, 3-homopiperazin-1-ylpropoxy, 2-pyrrolidin-1-ylethylamino, 3-pyrrolidin-1-ylpropylamino, 4-pyrrolidin-1-ylbutylamino, pyrrolidin-3-ylamino, pyrrolidin-2-ylmethylamino, 2-pyrrolidin-2-ylethylamino, 3-pyrrolidin-2-ylpropylamino, 2-morpholinoethylamino, 3-morpholinopropylamino, 30 4-morpholinobutylamino, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethylamino, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propylamino, 2-piperidinoethylamino, 3-piperidinopropylamino, 4-piperidinobutylamino, piperidin-3-ylamino, piperidin-4-ylamino, piperidin-3-ylmethylamino, 2-piperidin-3-ylethylamino, piperidin-4-ylmethylamino,

2-piperidin-4-ylethylamino, 2-homopiperidin-1-ylethylamino,
 3-homopiperidin-1-ylpropylamino, 2-(1,2,3,6-tetrahydropyridin-1-yl)ethylamino,
 3-(1,2,3,6-tetrahydropyridin-1-yl)propylamino, 4-(1,2,3,6-tetrahydropyridin-1-yl)butylamino,
 2-piperazin-1-ylethylamino, 3-piperazin-1-ylpropylamino, 4-piperazin-1-ylbutylamino,
 5 2-homopiperazin-1-ylethylamino or 3-homopiperazin-1-ylpropylamino,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R¹ substituent are optionally separated by the insertion into the chain of a group selected from O, NH, N(Me), CH=CH and C≡C,

and wherein any CH₂ or CH₃ group within a R¹ substituent optionally bears on each 10 said CH₂ or CH₃ group one or more fluoro or chloro groups or a substituent selected from hydroxy, amino, methoxy, methylsulphonyl, methylamino, dimethylamino, diisopropylamino, N-ethyl-N-methylamino, N-isopropyl-N-methylamino, N-methyl-N-propylamino, acetoxy, acetamido and N-methylacetamido,

and wherein any phenyl, imidazolyl, triazolyl, pyridyl or heterocyclyl group within a 15 substituent on R¹ optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, carbamoyl, methyl, ethyl, N-methylcarbamoyl, N,N-dimethylcarbamoyl and methoxy, and a pyrrolidin-2-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl or homopiperazin-1-yl group within a R¹ 20 substituent is optionally N-substituted with methyl, ethyl, propyl, allyl, 2-propynyl, methylsulphonyl, acetyl, 2-methoxyethyl, 3-methoxypropyl, cyanomethyl, 2-aminoethyl, 3-aminopropyl, 2-methylaminoethyl, 3-methylaminopropyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl, 2-fluoroethyl, 3-fluoropropyl, 2-chloroethyl, 3-chloropropyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, 2-morpholinoethyl, 3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, 2-piperazin-1-ylethyl or 3-piperazin-1-ylpropyl, the last 25 8 of which substituents each optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, methyl and methoxy,

and wherein any heterocyclyl group within a substituent on R¹ optionally bears 1 or 2 oxo substituents;

(o) n is 1 or 2 and the R³ groups, which may be the same or different, are selected from 30 halogeno, trifluoromethyl, cyano, hydroxy, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl and (1-6C)alkoxy;
 (p) n is 1 or 2 and the R³ groups, which may be the same or different, are located at the 3-, 5- 6-and/or 7-positions of the benzofuran-4-yl group and are selected from fluoro, chloro,

bromo, iodo, trifluoromethyl, cyano, hydroxy, methyl, ethyl, vinyl, allyl, isopropenyl, ethynyl, 1-propynyl, 2-propynyl, methoxy and ethoxy; and

(q) n is 1 and the R³ group is located at the 5- or 6-position of the benzofuran-4-yl group, especially the 5-position, and is selected from chloro, bromo, trifluoromethyl, cyano, hydroxy, 5 methyl, ethyl, methoxy and ethoxy.

Further particular novel compounds of the invention include, for example, quinoline derivatives of the Formula I, or pharmaceutically-acceptable salts thereof, wherein, unless otherwise stated, each of Z, m, R¹, n and R³ has any of the meanings defined hereinbefore provided that :-

10 (A) R¹ substituents may only be located at the 5-, 6- and/or 7-positions on the quinoline ring *i.e.* the 2- and 8-positions remain unsubstituted; or

(B) R¹ substituents may only be located at the 6- and/or 7-positions on the quinoline ring *i.e.* the 2-, 5- and 8-positions remain unsubstituted.

A particular compound of the invention is a quinoline derivative of the Formula I
15 wherein :

Z is O or NH;

m is 1 and the R¹ group is located at the 5-, 6- or 7-position or m is 2 and each R¹ group, which may be the same or different, is located at the 5- and 7-positions or at the 6- and 7-positions and R¹ is selected from hydroxy, amino, methyl, ethyl, propyl, butyl, methoxy, 20 ethoxy, propoxy, isopropoxy, butoxy, pent-4-nyloxy, hex-5-nyloxy, methylamino, ethylamino, dimethylamino, diethylamino, acetamido, propionamido, 2-imidazol-1-ylethoxy, 2-(1,2,4-triazol-1-yl)ethoxy, tetrahydrofuran-3-yloxy, tetrahydropyran-4-yloxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 4-pyrrolidin-1-ylbutoxy, pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy, 25 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 4-morpholinobutoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy, piperidin-3-yloxy, piperidin-4-yloxy, piperidin-3-ylmethoxy, piperidin-4-ylmethoxy, 2-piperidin-3-ylethoxy, 3-piperidin-3-ylpropoxy, 2-piperidin-4-ylethoxy, 30 3-piperidin-4-ylpropoxy, 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, 2-(1,2,3,6-tetrahydropyridin-1-yl)ethoxy, 3-(1,2,3,6-tetrahydropyridin-1-yl)propoxy, 4-(1,2,3,6-tetrahydropyridin-1-yl)butoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 4-piperazin-1-ylbutoxy, 2-homopiperazin-1-ylethoxy and 3-homopiperazin-1-ylpropoxy,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R¹ substituent are optionally separated by the insertion into the chain of a group selected from O, NH, N(Me), CH=CH and C≡C,

and wherein any CH₂ or CH₃ group within a R¹ substituent optionally bears on each 5 said CH₂ or CH₃ group one or more chloro groups or a substituent selected from hydroxy, amino, methoxy, methylsulphonyl, methylamino, dimethylamino, diethylamino, N-ethyl-N-methylamino, N-isopropyl-N-methylamino, N-methyl-N-propylamino and acetoxy; 10 and wherein any heteroaryl or heterocyclyl group within a substituent on R¹ optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, carbamoyl, methyl, ethyl, methoxy, N-methylcarbamoyl and N,N-dimethylcarbamoyl and a pyrrolidin-2-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl or homopiperazin-1-yl group within a R¹ substituent is optionally N-substituted with methyl, ethyl, propyl, allyl, prop-2-ynyl, methylsulphonyl, acetyl, 2-methoxyethyl, 3-methoxypropyl, cyanomethyl, 2-aminoethyl, 3-aminopropyl, 2-methylaminoethyl, 3-methylaminopropyl, 15 2-dimethylaminoethyl, 3-dimethylaminopropyl, 2-fluoroethyl, 3-fluoropropyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, 2-morpholinoethyl, 3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, 2-piperazin-1-ylethyl or 3-piperazin-1-ylpropyl, the last 8 of which substituents each optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, methyl and methoxy, 20 and wherein any heterocyclyl group within a substituent on R¹ optionally bears 1 or 2 oxo substituents; and

n is 0 or 1 and the R³ group, if present, is located at the 3-, 5-, 6- or 7-position of the benzofuran-4-yl group and is selected from fluoro, chloro, bromo, iodo, trifluoromethyl, cyano, hydroxy, methyl, ethyl, vinyl, allyl, ethynyl, methoxy and ethoxy; 25 or a pharmaceutically-acceptable acid-addition salt thereof.

A particular compound of the invention is a quinoline derivative of the Formula I wherein :

Z is O or NH;

m is 1 and the R¹ group is located at the 5-, 6- or 7-position or m is 2 and each R¹ 30 group, which may be the same or different, is located at the 5- and 7-positions or at the 6- and 7-positions and R¹ is selected from hydroxy, amino, methyl, ethyl, propyl, butyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, pent-4-ynyoxy, hex-5-ynyoxy, methylamino, ethylamino, dimethylamino, diethylamino, acetamido, propionamido, 2-imidazol-1-ylethoxy,

2-(1,2,4-triazol-1-yl)ethoxy, tetrahydrofuran-3-yloxy, tetrahydropyran-4-yloxy,
2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 4-pyrrolidin-1-ylbutoxy,
pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy,
3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 4-morpholinobutoxy,
5 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-
4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy,
piperidin-3-yloxy, piperidin-4-yloxy, piperidin-3-ylmethoxy, piperidin-4-ylmethoxy,
2-piperidin-3-ylethoxy, 3-piperidin-3-ylpropoxy, 2-piperidin-4-ylethoxy,
3-piperidin-4-ylpropoxy, 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy,
10 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 4-piperazin-1-ylbutoxy,
2-homopiperazin-1-ylethoxy and 3-homopiperazin-1-ylpropoxy,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R¹ substituent
are optionally separated by the insertion into the chain of a group selected from O, NH,
N(Me), CH=CH and C≡C,

15 and wherein any CH₂ or CH₃ group within a R¹ substituent optionally bears on each
said CH₂ or CH₃ group one or more chloro groups or a substituent selected from hydroxy,
amino, methoxy, methylsulphonyl, methylamino, dimethylamino, diethylamino,
N-ethyl-N-methylamino, N-isopropyl-N-methylamino, N-methyl-N-propylamino and acetoxy;
and wherein any heteroaryl or heterocyclyl group within a substituent on R¹ optionally
20 bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro,
trifluoromethyl, hydroxy, amino, carbamoyl, methyl, ethyl, methoxy, N-methylcarbamoyl and
N,N-dimethylcarbamoyl and a pyrrolidin-2-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl or
homopiperazin-1-yl group within a R¹ substituent is optionally N-substituted with allyl,
methylsulphonyl, acetyl, 2-methoxyethyl, 3-methoxypropyl, cyanomethyl, 2-aminoethyl,
25 3-aminopropyl, 2-methylaminoethyl, 3-methylaminopropyl, 2-dimethylaminoethyl,
3-dimethylaminopropyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, 2-morpholinoethyl,
3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, 2-piperazin-1-ylethyl or
3-piperazin-1-ylpropyl, the last 8 of which substituents each optionally bears 1 or 2
substituents, which may be the same or different, selected from fluoro, chloro, methyl and
30 methoxy,

and wherein any heterocyclyl group within a substituent on R¹ optionally bears 1 or 2
oxo substituents; and

n is 0 or 1 and the R³ group, if present, is located at the 3-, 5- or 6-position of the benzofuran-4-yl group and is selected from fluoro, chloro, bromo, trifluoromethyl, cyano, hydroxy, methyl, ethyl, vinyl, allyl, ethynyl, methoxy and ethoxy; or a pharmaceutically-acceptable acid-addition salt thereof.

5 A further particular compound of the invention is a quinoline derivative of the Formula I wherein :

Z is O or NH;

m is 2 and the first R¹ group is located at the 6-position and is selected from hydroxy, methoxy, ethoxy and propoxy, and the second R¹ group is located at the 7-position and is 10 selected from 2-hydroxyethoxy, 3-hydroxypropoxy, 4-hydroxybutoxy, 2-methoxyethoxy, 3-methoxypropoxy, 4-methoxybutoxy, 2-(2-hydroxyethoxy)ethoxy, 2-(2-methoxyethoxy)ethoxy, 2-dimethylaminoethoxy, 3-dimethylaminoproxy, 4-dimethylaminobutoxy, 2-diethylaminoethoxy, 3-diethylaminoproxy, 4-diethylaminobutoxy, 2-diisopropylaminoethoxy, 3-diisopropylaminoproxy, 15 4-diisopropylaminobutoxy, 2-(N-isopropyl-N-methylamino)ethoxy, 3-(N-isopropyl-N-methylamino)propoxy, 4-(N-isopropyl-N-methylamino)butoxy, 2-(N-allylamino)ethoxy, 3-(N-allylamino)propoxy, 2-(N-allyl-N-methylamino)ethoxy, 3-(N-allyl-N-methylamino)propoxy, 2-(N-prop-2-ynylamino)ethoxy, 3-(N-prop-2-ynylamino)propoxy, 2-(N-methyl-N-prop-2-ynylamino)ethoxy, 20 3-(N-methyl-N-prop-2-ynylamino)propoxy, 2-pyrrolidin-1-yloxy, 3-pyrrolidin-1-ylpropoxy, 4-pyrrolidin-1-ylbutoxy, pyrrolidin-3-yloxy, N-methylpyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-yloxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinoproxy, 4-morpholinobutoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin- 25 4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy, piperidin-3-yloxy, N-methylpiperidin-3-yloxy, piperidin-4-yloxy, N-methylpiperidin-4-yloxy, piperidin-3-ylmethoxy, N-methylpiperidin-3-ylmethoxy, piperidin-4-ylmethoxy, N-methylpiperidin-4-ylmethoxy, 2-piperidin-3-yloxy, 2-(N-methylpiperidin-3-yl)ethoxy, 3-piperidin-3-ylpropoxy, 3-(N-methylpiperidin-3-yl)propoxy, 2-piperidin-4-yloxy, 30 2-(N-methylpiperidin-4-yl)ethoxy, 3-piperidin-4-ylpropoxy, 3-(N-methylpiperidin-4-yl)propoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 2-(4-allylpiperazin-1-yl)ethoxy, 3-(4-allylpiperazin-1-yl)propoxy,

4-(4-allylpiperazin-1-yl)butoxy, 2-(4-methylsulphonylpiperazin-1-yl)ethoxy,
 3-(4-methylsulphonylpiperazin-1-yl)propoxy, 4-(4-methylsulphonylpiperazin-1-yl)butoxy,
 2-(4-acetyl
 4-(4-acetyl
 5 3-(4-cyanomethyl
 2-[2-(4-methyl
 2-methylsulphonylethoxy and 3-methylsulphonylpropoxy,

and wherein any CH_2 group within the second R^1 group that is attached to two carbon atoms optionally bears a hydroxy group or acetoxy group on said CH_2 group,

10 and wherein any heterocyclyl group within the second R^1 group optionally bears 1 or 2 substituents selected from fluoro, hydroxy, methyl and oxo; and

n is 0 or n is 1 and the R^3 group, if present, is located at the 5- or 6-position of the benzofuran-4-yl group and is selected from fluoro, chloro, bromo, trifluoromethyl, cyano, methyl, ethyl, ethynyl, methoxy and ethoxy;

15 or a pharmaceutically-acceptable acid-addition salt thereof.

A further particular compound of the invention is a quinoline derivative of the Formula I wherein :

Z is O or NH;

m is 2 and the first R^1 group is a 6-methoxy group and the second R^1 group is located
 20 at the 7-position and is selected from 2-dimethylaminoethoxy, 3-dimethylaminopropoxy,
 4-dimethylaminobutoxy, 2-diethylaminoethoxy, 3-diethylaminopropoxy,
 4-diethylaminobutoxy, 2-diisopropylaminoethoxy, 3-diisopropylaminopropoxy,
 4-diisopropylaminobutoxy, 2-(N-isopropyl-N-methylamino)ethoxy,
 3-(N-isopropyl-N-methylamino)propoxy, 4-(N-isopropyl-N-methylamino)butoxy,
 25 2-(N-isobutyl-N-methylamino)ethoxy, 3-(N-isobutyl-N-methylamino)propoxy,
 4-(N-isobutyl-N-methylamino)butoxy, 2-(N-allyl-N-methylamino)ethoxy,
 3-(N-allyl-N-methylamino)propoxy, 2-(N-prop-2-ynylamino)ethoxy,
 3-(N-prop-2-ynylamino)propoxy, 2-(N-methyl-N-prop-2-ynylamino)ethoxy,
 3-(N-methyl-N-prop-2-ynylamino)propoxy, 2-pyrrolidin-1-ylethoxy,
 30 3-pyrrolidin-1-ylpropoxy, 4-pyrrolidin-1-ylbutoxy, pyrrolidin-3-yloxy,
N-methylpyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy,
 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 4-morpholinobutoxy,
 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-

4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy, piperidin-3-yloxy, N-methylpiperidin-3-yloxy, piperidin-4-yloxy, N-methylpiperidin-4-yloxy, piperidin-3-ylmethoxy, N-methylpiperidin-3-ylmethoxy, N-cyanomethylpiperidin-3-ylmethoxy, piperidin-4-ylmethoxy,

5 N-methylpiperidin-4-ylmethoxy, N-cyanomethylpiperidin-4-ylmethoxy, 2-piperidin-3-ylethoxy, 2-(N-methylpiperidin-3-yl)ethoxy, 3-piperidin-3-ylpropoxy, 3-(N-methylpiperidin-3-yl)propoxy, 2-piperidin-4-ylethoxy, 2-(N-methylpiperidin-4-yl)ethoxy, 3-piperidin-4-ylpropoxy, 3-(N-methylpiperidin-4-yl)propoxy, 2-(4-hydroxypiperidin-1-yl)ethoxy,

10 3-(4-hydroxypiperidin-1-yl)propoxy, 4-(4-hydroxypiperidin-1-yl)butoxy, 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, 4-homopiperidin-1-ylbutoxy, 2-(1,2,3,6-tetrahydropyridin-1-yl)ethoxy, 3-(1,2,3,6-tetrahydropyridin-1-yl)propoxy, 4-(1,2,3,6-tetrahydropyridin-1-yl)butoxy, 2-piperazin-1-ylethoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 3-piperazin-1-ylpropoxy,

15 3-(4-methylpiperazin-1-yl)propoxy, 4-piperazin-1-ylbutoxy, 4-(4-methylpiperazin-1-yl)butoxy, 2-(4-allylpiperazin-1-yl)ethoxy, 3-(4-allylpiperazin-1-yl)propoxy, 2-(4-prop-2-ynylpiperazin-1-yl)ethoxy, 3-(4-prop-2-ynylpiperazin-1-yl)propoxy, 4-(4-prop-2-ynylpiperazin-1-yl)butoxy, 2-(4-methylsulphonylpiperazin-1-yl)ethoxy,

20 3-(4-methylsulphonylpiperazin-1-yl)propoxy, 4-(4-methylsulphonylpiperazin-1-yl)butoxy, 2-(4-acetyl piperazin-1-yl)ethoxy, 3-(4-acetyl piperazin-1-yl)propoxy, 4-(4-acetyl piperazin-1-yl)butoxy, 2-[4-(2-fluoroethyl)piperazin-1-yl]ethoxy, 3-[4-(2-fluoroethyl)piperazin-1-yl]propoxy, 4-[4-(2-fluoroethyl)piperazin-1-yl]butoxy, 2-(4-cyanomethylpiperazin-1-yl)ethoxy, 3-(4-cyanomethylpiperazin-1-yl)propoxy,

25 4-(4-cyanomethylpiperazin-1-yl)butoxy, 2-(2-piperazin-1-ylethoxy)ethoxy, 2-[2-(4-methylpiperazin-1-yl)ethoxy]ethoxy, 2-chloroethoxy, 3-chloropropoxy, 4-chlorobutoxy, 2-methylsulphonylethoxy, 3-methylsulphonylpropoxy, 2-tetrahydropyran-4-ylethoxy, 3-tetrahydropyran-4-ylpropoxy, 2-pyrrol-1-ylethoxy, 3-pyrrol-1-ylpropoxy, 2-(2-pyridyloxy)ethoxy, 3-(2-pyridyloxy)propoxy,

30 2-(3-pyridyloxy)ethoxy, 3-(3-pyridyloxy)propoxy, 2-(4-pyridyloxy)ethoxy, 3-(4-pyridyloxy)propoxy, 2-pyridylmethoxy, 3-pyridylmethoxy and 4-pyridylmethoxy, and wherein any CH₂ group within the second R¹ group that is attached to two carbon atoms optionally bears a hydroxy group on said CH₂ group,

and wherein any heteroaryl group within the second R¹ group optionally bears 1 or 2 substituents selected from chloro, cyano, hydroxy and methyl, and any heterocyclyl group within the second R¹ group optionally bears 1 or 2 substituents selected from fluoro, hydroxy, methyl and oxo; and

5 n is 0 or n is 1 and the R³ group, if present, is located at the 5-, 6- or 7-position of the benzofuran-4-yl group and is selected from fluoro, chloro, bromo, iodo and cyano; or a pharmaceutically-acceptable acid-addition salt thereof.

A further particular compound of the invention is a quinoline derivative of the Formula I wherein :

10 Z is O or NH;

m is 2 and the first R¹ group is a 6-methoxy group and the second R¹ group is located at the 7-position and is selected from 2-dimethylaminoethoxy, 3-dimethylaminoproxy, 4-dimethylaminobutoxy, 2-diethylaminoethoxy, 3-diethylaminoproxy, 4-diethylaminobutoxy, 2-diisopropylaminoethoxy, 3-diisopropylaminoproxy, 15 4-diisopropylaminobutoxy, 2-(N-isopropyl-N-methylamino)ethoxy, 3-(N-isopropyl-N-methylamino)prooxy, 4-(N-isopropyl-N-methylamino)butoxy, 2-(N-isobutyl-N-methylamino)ethoxy, 3-(N-isobutyl-N-methylamino)prooxy, 4-(N-isobutyl-N-methylamino)butoxy, 2-(N-allyl-N-methylamino)ethoxy, 3-(N-allyl-N-methylamino)prooxy, 2-(N-prop-2-ynylamino)ethoxy, 20 3-(N-prop-2-ynylamino)prooxy, 2-(N-methyl-N-prop-2-ynylamino)ethoxy, 3-(N-methyl-N-prop-2-ynylamino)prooxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylprooxy, 4-pyrrolidin-1-ylbutoxy, pyrrolidin-3-yloxy, N-methylpyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylprooxy, 2-morpholinoethoxy, 3-morpholinoproxy, 4-morpholinobutoxy, 25 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)prooxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy, piperidin-3-yloxy, N-methylpiperidin-3-yloxy, piperidin-4-yloxy, N-methylpiperidin-4-yloxy, piperidin-3-ylmethoxy, N-methylpiperidin-3-ylmethoxy, N-cyanomethylpiperidin-3-ylmethoxy, piperidin-4-ylmethoxy, 30 N-methylpiperidin-4-ylmethoxy, N-cyanomethylpiperidin-4-ylmethoxy, 2-piperidin-3-ylethoxy, 2-(N-methylpiperidin-3-yl)ethoxy, 3-piperidin-3-ylprooxy, 3-(N-methylpiperidin-3-yl)prooxy, 2-piperidin-4-ylethoxy, 2-(N-methylpiperidin-4-yl)ethoxy, 3-piperidin-4-ylprooxy,

3-(N-methylpiperidin-4-yl)propoxy, 2-homopiperidin-1-ylethoxy,
 3-homopiperidin-1-ylpropoxy, 4-homopiperidin-1-ylbutoxy, 2-piperazin-1-ylethoxy,
 2-(4-methylpiperazin-1-yl)ethoxy, 3-piperazin-1-ylpropoxy,
 3-(4-methylpiperazin-1-yl)propoxy, 4-piperazin-1-ylbutoxy,
 5 4-(4-methylpiperazin-1-yl)butoxy, 2-(4-allylpiperazin-1-yl)ethoxy,
 3-(4-allylpiperazin-1-yl)propoxy, 4-(4-allylpiperazin-1-yl)butoxy,
 2-(4-methylsulphonylpiperazin-1-yl)ethoxy, 3-(4-methylsulphonylpiperazin-1-yl)propoxy,
 4-(4-methylsulphonylpiperazin-1-yl)butoxy, 2-(4-acetyl
 3-(4-acetyl
 10 2-(4-cyanomethyl
 4-(4-cyanomethyl
 2-[2-(4-methylpiperazin-1-yl)ethoxy]ethoxy, 2-chloroethoxy, 3-chloropropoxy,
 2-methylsulphonylethoxy, 3-methylsulphonylpropoxy, 2-tetrahydropyran-4-ylethoxy,
 3-tetrahydropyran-4-ylpropoxy, 2-pyrrol-1-ylethoxy, 3-pyrrol-1-ylpropoxy,
 15 2-(2-pyridyloxy)ethoxy, 3-(2-pyridyloxy)propoxy, 2-(3-pyridyloxy)ethoxy,
 3-(3-pyridyloxy)propoxy, 2-(4-pyridyloxy)ethoxy, 3-(4-pyridyloxy)propoxy,
 2-pyridylmethoxy, 3-pyridylmethoxy and 4-pyridylmethoxy,
 and wherein any CH₂ group within the second R¹ group that is attached to two carbon
 atoms optionally bears a hydroxy group on said CH₂ group,
 20 and wherein any heteroaryl group within the second R¹ group optionally bears 1 or 2
 substituents selected from chloro, cyano, hydroxy and methyl, and any heterocyclyl group
 within the second R¹ group optionally bears 1 or 2 substituents selected from fluoro, hydroxy,
 methyl and oxo; and
 n is 0 or n is 1 and the R³ group, if present, is located at the 6-position of the
 25 benzofuran-4-yl group and is selected from fluoro, chloro and bromo;
 or a pharmaceutically-acceptable acid-addition salt thereof.

A further particular compound of the invention is a quinoline derivative of the
 Formula I wherein :

Z is NH;

30 m is 2 and the first R¹ group is a 6-methoxy group and the second R¹ group is located
 at the 7-position and is selected from 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy,
 2-morpholinoethoxy, 3-morpholinopropoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-
 4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy,

3-piperidinopropoxy, piperidin-3-ylmethoxy, N-methylpiperidin-3-ylmethoxy, piperidin-4-ylmethoxy, N-methylpiperidin-4-ylmethoxy, 2-piperidin-3-ylethoxy, 2-(N-methylpiperidin-3-yl)ethoxy, 3-piperidin-3-ylpropoxy, 3-(N-methylpiperidin-3-yl)propoxy, 2-piperidin-4-ylethoxy, 2-(N-methylpiperidin-4-yl)ethoxy,

5 3-piperidin-4-ylpropoxy, 3-(N-methylpiperidin-4-yl)propoxy, 2-(1,2,3,6-tetrahydropyridin-1-yl)ethoxy, 3-(1,2,3,6-tetrahydropyridin-1-yl)propoxy, 4-(1,2,3,6-tetrahydropyridin-1-yl)butoxy, 2-(4-hydroxypiperidin-1-yl)ethoxy, 3-(4-hydroxypiperidin-1-yl)propoxy, 4-(4-hydroxypiperidin-1-yl)butoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 4-piperazin-1-ylbutoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 4-(4-methylpiperazin-1-yl)butoxy, 3-(4-allylpiperazin-1-yl)propoxy, 3-(4-prop-2-ynylpiperazin-1-yl)propoxy, 3-(4-methylsulphonylpiperazin-1-yl)propoxy, 3-(4-acetyl

piperazin-1-yl)propoxy, 4-(4-acetyl

piperazin-1-yl)butoxy, 3-[4-(2-fluoroethyl)piperazin-1-yl]propoxy, 2-(4-cyanomethylpiperazin-1-yl)ethoxy, 3-(4-cyanomethylpiperazin-1-yl)propoxy, 2-[2-(4-methylpiperazin-1-yl)ethoxy]ethoxy,

15 3-chloropropoxy, 4-chlorobutoxy, 2-methylsulphonylethoxy, 3-methylsulphonylpropoxy, 2-(2-methoxyethoxy)ethoxy, 2-(4-pyridyloxy)ethoxy, 3-pyridylmethoxy and 2-cyanopyrid-4-ylmethoxy; and

n is 0 or n is 1 and the R³ group, if present, is located at the 5-, 6- or 7-position of the benzofuranyl group and is selected from fluoro, chloro, bromo and iodo;

20 or a pharmaceutically-acceptable acid-addition salt thereof.

A further particular compound of the invention is a quinoline derivative of the Formula I wherein :

Z is NH;

m is 2 and the first R¹ group is a 6-methoxy group and the second R¹ group is located

25 at the 7-position and is selected from 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, piperidin-3-ylmethoxy, N-methylpiperidin-3-ylmethoxy, piperidin-4-ylmethoxy, N-methylpiperidin-4-ylmethoxy, 2-piperidin-3-ylethoxy,

30 2-(N-methylpiperidin-3-yl)ethoxy, 3-piperidin-3-ylpropoxy, 3-(N-methylpiperidin-3-yl)propoxy, 2-piperidin-4-ylethoxy, 2-(N-methylpiperidin-4-yl)ethoxy, 3-piperidin-4-ylpropoxy, 3-(N-methylpiperidin-4-yl)propoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy,

3-(4-allylpiperazin-1-yl)propoxy, 3-(4-methylsulphonylpiperazin-1-yl)propoxy,
 3-(4-acetyl
 3-(4-cyanomethyl
 3-chloropropoxy, 2-methylsulphonylethoxy, 3-methylsulphonylpropoxy,
 5 2-(4-pyridyloxy)ethoxy, 3-pyridylmethoxy and 2-cyanopyrid-4-ylmethoxy; and

n is 0 or n is 1 and the R³ group, if present, is located at the 6-position of the benzofuranyl group and is selected from chloro and bromo;
 or a pharmaceutically-acceptable acid-addition salt thereof.

A further particular compound of the invention is a quinoline derivative of the

10 Formula I wherein :

Z is NH;

m is 2 and the first R¹ group is a 6-methoxy group and the second R¹ group is located at the 7-position and is selected from methoxy, ethoxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy,
 15 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-(1,2,3,6-tetrahydropyridin-1-yl)ethoxy, 3-(1,2,3,6-tetrahydropyridin-1-yl)propoxy, 4-(1,2,3,6-tetrahydropyridin-1-yl)butoxy, 2-(4-hydroxypiperidin-1-yl)ethoxy, 3-(4-hydroxypiperidin-1-yl)propoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-(4-methyl
 20 3-(4-methyl
 25 2-methylsulphonylethoxy, 3-methylsulphonylpropoxy and 2-(2-methoxyethoxy)ethoxy; and n is 0 or n is 1 and the R³ group, if present, is located at the 5- or 6-position of the benzofuranyl group and is selected from fluoro, chloro, bromo and iodo;
 or a pharmaceutically-acceptable acid-addition salt thereof.

A further particular compound of the invention is a quinoline derivative of the

30 Formula I wherein :

Z is NH;

m is 2 and the first R¹ group is a 6-methoxy group and the second R¹ group is located at the 7-position and is selected from methoxy, 3-morpholinopropoxy,

3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 3-(1,2,3,6-tetrahydropyridin-1-yl)propoxy, 4-(1,2,3,6-tetrahydropyridin-1-yl)butoxy,
 3-(4-hydroxypiperidin-1-yl)propoxy, 3-piperazin-1-ylpropoxy,
 3-(4-methylpiperazin-1-yl)propoxy, 4-(4-methylpiperazin-1-yl)butoxy,
 5 3-(4-prop-2-ynylpiperazin-1-yl)propoxy, 3-(4-acetyl
 4-(4-acetyl
 3-chloropropoxy, 4-chlorobutoxy and 2-(2-methoxyethoxy)ethoxy; and
 n is 0 or n is 1 and the R³ group, if present, is located at the 5- or 6-position of the
 benzofuranyl group and is selected from fluoro, chloro and bromo;
 10 or a pharmaceutically-acceptable acid-addition salt thereof.

A further particular compound of the invention is a quinoline derivative of the
 Formula I wherein :

Z is NH;

m is 2 and the first R¹ group is a 6-methoxy group and the second R¹ group is located
 15 at the 7-position and is selected from 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy,
 2-morpholinoethoxy, 3-morpholinopropoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy,
 3-piperidinopropoxy, piperidin-3-ylmethoxy, N-methylpiperidin-3-ylmethoxy,
 piperidin-4-ylmethoxy, N-methylpiperidin-4-ylmethoxy, 2-piperidin-3-ylethoxy,
 20 2-(N-methylpiperidin-3-yl)ethoxy, 3-piperidin-3-ylpropoxy, 3-(N-methylpiperidin-3-yl)propoxy, 2-piperidin-4-ylethoxy, 2-(N-methylpiperidin-4-yl)ethoxy,
 3-piperidin-4-ylpropoxy, 3-(N-methylpiperidin-4-yl)propoxy,
 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy,
 2-(4-cyanomethylpiperazin-1-yl)ethoxy, 3-(4-cyanomethylpiperazin-1-yl)propoxy,
 25 2-[2-(4-methylpiperazin-1-yl)ethoxy]ethoxy, 3-chloropropoxy, 2-methylsulphonylethoxy,
 3-methylsulphonylpropoxy, 2-(4-pyridyloxy)ethoxy, 3-pyridylmethoxy and
 2-cyanopyrid-4-ylmethoxy; and
 n is 0 or n is 1 and the R³ group, if present, is located at the 6-position of the
 benzofuran-4-yl group and is selected from chloro and bromo;
 30 or a pharmaceutically-acceptable acid-addition salt thereof.

A further particular compound of the invention is a quinoline derivative of the
 Formula I wherein :

Z is NH;

m is 2 and the first R¹ group is a 6-methoxy group and the second R¹ group is located at the 7-position and is selected from 3-(4-methylpiperazin-1-yl)propoxy,

n is 1 and the R³ group is a chloro or bromo group located at the 6-position of the benzofuran-4-yl group;

5 or a pharmaceutically-acceptable acid-addition salt thereof.

A particular compound of the invention is, for example, a quinoline derivative of the Formula I selected from :-

4-(6-chlorobenzofuran-4-ylamino)-3-cyano-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinoline and

10 4-benzofuran-7-ylamino-3-cyano-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinoline, or a pharmaceutically-acceptable acid-addition salt thereof.

A further particular compound of the invention is a quinoline derivative of the Formula I wherein :

Z is O or NH;

15 m is 1 and the R¹ group is located at the 5-position and is selected from tetrahydrofuran-3-yloxy, tetrahydropyran-4-yloxy, tetrahydrothien-3-yloxy, 1,1-dioxotetrahydrothien-3-yloxy, tetrahydrothiopyran-4-yloxy, 1,1-dioxotetrahydrothiopyran-4-yloxy, N-methylazetidin-3-yloxy, N-ethylazetidin-3-yloxy, N-isopropylazetidin-3-yloxy, pyrrolidin-3-yloxy, N-methylpyrrolidin-3-yloxy, 20 pyrrolidin-2-ylmethoxy, 3-piperidinyloxy, N-methylpiperidin-3-yloxy, 4-piperidinyloxy, N-methylpiperidin-4-yloxy, N-allylpiperidin-4-yloxy, N-prop-2-ynylpiperidin-4-yloxy, N-acetyl

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piperidin-4-yloxy, N-methylsulphonylpiperidin-4-yloxy, N-(2-methoxyethyl)piperidin-4-yloxy, piperidin-3-ylmethoxy, N-methylpiperidin-3-ylmethoxy, piperidin-4-ylmethoxy, N-methylpiperidin-4-ylmethoxy, 25 cyclobutyloxy, cyclopentyloxy and cyclohexyloxy,

or m is 2 and the first R¹ group is located at the 5-position and is selected from the group of substituents listed immediately above and the second R¹ group is located at the 7-position and is selected from hydroxy, methoxy, ethoxy, propoxy, isopropoxy, isobutoxy, 2-fluoroethoxy, 2,2,2-trifluoroethoxy, benzyloxy, 2-pyrrolidin-1-yethoxy, 30 3-pyrrolidin-1-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-piperidin-4-yethoxy, 2-(N-methylpiperidin-4-yl)ethoxy, 2-homopiperidin-1-yethoxy,

3-homopiperidin-1-ylpropoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy,
2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy,
3-(4-cyanomethylpiperazin-1-yl)propoxy, 2-[(2S)-2-carbamoylpyrrolidin-1-yl]ethoxy,
2-[(2S)-2-(N-methylcarbamoyl)pyrrolidin-1-yl]ethoxy,
5 2-[(2S)-2-(N,N-dimethylcarbamoyl)pyrrolidin-1-yl]ethoxy, 2-tetrahydropyran-4-ylethoxy,
2-hydroxyethoxy, 3-hydroxypropoxy, 2-methoxyethoxy, 3-methoxypropoxy,
2-methylsulphonylethoxy, 3-methylsulphonylpropoxy, 2-(2-methoxyethoxy)ethoxy,
piperidin-4-ylmethoxy, N-methylpiperidin-4-ylmethoxy, 2-(4-pyridyloxy)ethoxy,
2-pyridylmethoxy, 3-pyridylmethoxy, 4-pyridylmethoxy and 3-cyanopyrid-4-ylmethoxy;
10 and wherein any CH₂ group within a R¹ substituent that is attached to two carbon atoms optionally bears a hydroxy group on said CH₂ group, and wherein any heterocyclyl group within a R¹ substituent optionally bears 1 or 2 oxo substituents,
and wherein any CH₂ group within a R¹ substituent that is attached to two carbon atoms optionally bears a hydroxy group on said CH₂ group;
15 n is 0 or n is 1 and the R³ group, if present is located at the 3-, 5-, 6- or 7-position of the benzofuran-4-yl group and is selected from fluoro, chloro, bromo, trifluoromethyl, cyano, methyl, ethyl, ethynyl, methoxy and ethoxy;
or a pharmaceutically-acceptable acid-addition salt thereof.

A further particular compound of the invention is a quinoline derivative of the
20 Formula I wherein :

m is 2 and the first R¹ group is located at the 5-position and is selected from tetrahydrofuran-3-yloxy, tetrahydropyran-4-yloxy, tetrahydrothien-3-yloxy, 1,1-dioxotetrahydrothien-3-yloxy, tetrahydrothiopyran-4-yloxy, 1,1-dioxotetrahydrothiopyran-4-yloxy, N-methylazetidin-3-yloxy, N-ethylazetidin-3-yloxy,
25 N-isopropylazetidin-3-yloxy, pyrrolidin-3-yloxy, N-methylpyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 3-piperidinyloxy, N-methylpiperidin-3-yloxy, 4-piperidinyloxy, N-methylpiperidin-4-yloxy, N-allylpiperidin-4-yloxy, N-prop-2-ynylpiperidin-4-yloxy, N-acetyl piperidin-4-yloxy, N-methylsulphonylpiperidin-4-yloxy, N-(2-methoxyethyl)piperidin-4-yloxy, piperidin-3-ylmethoxy,
30 N-methylpiperidin-3-ylmethoxy, piperidin-4-ylmethoxy, N-methylpiperidin-4-ylmethoxy, cyclobutyloxy, cyclopentyloxy and cyclohexyloxy,
and the second R¹ is located at the 7-position and is selected from hydroxy, methoxy, ethoxy, propoxy, isopropoxy, isobutoxy, 2-fluoroethoxy, 2,2,2-trifluoroethoxy, benzyloxy,

2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 2-morpholinoethoxy,
 3-morpholinopropoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy,
 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy,
 3-piperidinopropoxy, 2-piperidin-4-ylethoxy, 2-(N-methylpiperidin-4-yl)ethoxy,

5 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, 2-piperazin-1-ylethoxy,
 3-piperazin-1-ylpropoxy, 2-(4-methylpiperazin-1-yl)ethoxy,
 3-(4-methylpiperazin-1-yl)propoxy, 3-(4-cyanomethylpiperazin-1-yl)propoxy,
 2-[(2S)-2-carbamoylpyrrolidin-1-yl]ethoxy, 2-[(2S)-2-(N-methylcarbamoyl)pyrrolidin-1-
 yl]ethoxy, 2-[(2S)-2-(N,N-dimethylcarbamoyl)pyrrolidin-1-yl]ethoxy,

10 2-tetrahydropyran-4-ylethoxy, 2-hydroxyethoxy, 3-hydroxypropoxy, 2-methoxyethoxy,
 3-methoxypropoxy, 2-methylsulphonylethoxy, 3-methylsulphonylpropoxy,
 2-(2-methoxyethoxy)ethoxy, piperidin-4-ylmethoxy, N-methylpiperidin-4-ylmethoxy,
 2-(4-pyridyloxy)ethoxy, 2-pyridylmethoxy, 3-pyridylmethoxy, 4-pyridylmethoxy and
 3-cyanopyrid-4-ylmethoxy;

15 and wherein any CH₂ group within a R¹ substituent that is attached to two carbon
 atoms optionally bears a hydroxy group on said CH₂ group, and wherein any heterocyclyl
 group within a R¹ substituent optionally bears 1 or 2 oxo substituents,
 and wherein any CH₂ group within a R¹ substituent that is attached to two carbon
 atoms optionally bears a hydroxy group on said CH₂ group;

20 n is 0 or n is 1 and the R³ group, if present is located at the 3-, 5- or 6-position of the
 benzofuran-4-yl group and is selected from fluoro, chloro, bromo, trifluoromethyl, cyano,
 methyl, ethyl, ethynyl, methoxy and ethoxy;
 or a pharmaceutically-acceptable acid-addition salt thereof.

A further particular compound of the invention is a quinoline derivative of the

25 Formula I wherein :

m is 2 and the first R¹ group is located at the 5-position and is selected from
 tetrahydropyran-4-yloxy, N-methylpyrrolidin-3-yloxy, 4-piperidinyloxy,
N-methylpiperidin-4-yloxy, piperidin-4-ylmethoxy and N-methylpiperidin-4-ylmethoxy,
 and the second R¹ is located at the 7-position and is selected from methoxy,

30 benzyloxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 2-piperidinoethoxy,
 3-piperidinopropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-(4-methylpiperazin-
 1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy and 3-methylsulphonylpropoxy;

n is 0 or n is 1 and the R³ group, if present, is located at the 6-position of the benzofuran-4-yl group and is selected from chloro and bromo; or a pharmaceutically-acceptable acid-addition salt thereof.

A further particular compound of the invention is a quinoline derivative of the

5 Formula I wherein :

m is 2 and the first R¹ group is located at the 5-position and is selected from tetrahydropyran-4-yloxy, 4-piperidinyloxy, N-methylpiperidin-4-yloxy, piperidin-4-ylmethoxy and N-methylpiperidin-4-ylmethoxy, and the second R¹ is located at the 7-position and is selected from methoxy, ethoxy, propoxy, 10 isopropoxy, isobutoxy, 2-fluoroethoxy, 2,2,2-trifluoroethoxy, benzyloxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 3-(4-hydroxypiperidin-1-yl)propoxy, 2-piperidin-4-ylethoxy, 2-(N-methylpiperidin-4-yl)ethoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 15 3-(4-methylpiperazin-1-yl)propoxy, 3-(4-cyanomethylpiperazin-1-yl)propoxy, 3-methylsulphonylpropoxy, piperidin-4-ylmethoxy and N-methylpiperidin-4-ylmethoxy; n is 0 or n is 1 and the R³ group, if present, is located at the 6-position of the benzofuran-4-yl group and is selected from chloro and bromo; or a pharmaceutically-acceptable acid-addition salt thereof.

20 A further particular compound of the invention is a quinoline derivative of the

Formula I wherein :

Z is NH;

m is 1 and the R¹ group is located at the 5-position and is selected from tetrahydropyran-4-yloxy, 4-piperidinyloxy and N-methylpiperidin-4-yloxy, 25 or m is 2 and the first R¹ group is located at the 5-position and is selected from tetrahydropyran-4-yloxy, 4-piperidinyloxy and N-methylpiperidin-4-yloxy, and the second R¹ group is located at the 7-position and is selected from methoxy, ethoxy, propoxy, 3-pyrrolidin-1-ylpropoxy, 3-piperidinopropoxy, 3-morpholinopropoxy, 3-piperazin-1-ylpropoxy and 3-(4-methylpiperazin-1-yl)propoxy; 30 n is 0 or n is 1 and the R³ group, if present, is a chloro group located at the 5-position of the benzofuran-4-yl group; or a pharmaceutically-acceptable acid-addition salt thereof.

A further particular compound of the invention is a quinoline derivative of the Formula I wherein :

Z is NH;

m is 1 and the R¹ group is located at the 5-position and is selected from

5 tetrahydropyran-4-yloxy and N-methylpiperidin-4-yloxy,

or m is 2 and the first R¹ group is located at the 5-position and is selected from tetrahydropyran-4-yloxy and N-methylpiperidin-4-yloxy, and the second R¹ group is located at the 7-position and is selected from methoxy and 3-morpholinopropoxy; and

n is 0;

10 or a pharmaceutically-acceptable acid-addition salt thereof.

A further particular compound of the invention is, for example, a quinoline derivative of the Formula I selected from:-

4-(6-chlorobenzofuran-4-ylamino)-3-cyano-7-methoxy-5-(N-methylpiperidin-4-yloxy)quinoline,

15 4-(6-chlorobenzofuran-4-ylamino)-3-cyano-7-(2-pyrrolidin-1-ylethoxy)-5-tetrahydropyran-4-yloxyquinoline,

4-(6-chlorobenzofuran-4-ylamino)-3-cyano-7-(3-pyrrolidin-1-ylpropoxy)-5-tetrahydropyran-4-yloxyquinoline,

4-(6-chlorobenzofuran-4-ylamino)-3-cyano-7-[3-(4-methylpiperazin-1-yl)propoxy]-

20 5-tetrahydropyran-4-yloxyquinoline,

4-(6-chlorobenzofuran-4-ylamino)-3-cyano-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinoline,

4-(6-chlorobenzofuran-4-ylamino)-3-cyano-7-(2-piperidinoethoxy)-5-tetrahydropyran-4-yloxyquinoline and

25 4-(6-chlorobenzofuran-4-ylamino)-3-cyano-7-(N-methylpiperidin-4-ylmethoxy)-5-tetrahydropyran-4-yloxyquinoline;

or a pharmaceutically-acceptable acid-addition salt thereof.

A further particular compound of the invention is, for example, a quinoline derivative of the Formula I selected from:-

30 4-(5-chlorobenzofuran-4-ylamino)-3-cyano-7-methoxy-5-(N-methylpiperidin-4-yloxy)quinoline,

4-(5-chlorobenzofuran-4-ylamino)-3-cyano-7-(2-pyrrolidin-1-ylethoxy)-5-tetrahydropyran-4-yloxyquinoline,

4-(5-chlorobenzofuran-4-ylamino)-3-cyano-7-(3-pyrrolidin-1-ylpropoxy)-5-tetrahydropyran-4-yloxyquinoline,

4-(5-chlorobenzofuran-4-ylamino)-3-cyano-7-[3-(4-methylpiperazin-1-yl)propoxy]-5-tetrahydropyran-4-yloxyquinoline,

5 4-(5-chlorobenzofuran-4-ylamino)-3-cyano-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinoline,

4-(5-chlorobenzofuran-4-ylamino)-3-cyano-7-(2-piperidinoethoxy)-5-tetrahydropyran-4-yloxyquinoline and

4-(5-chlorobenzofuran-4-ylamino)-3-cyano-7-(N-methylpiperidin-4-ylmethoxy)-

10 5-tetrahydropyran-4-yloxyquinoline;

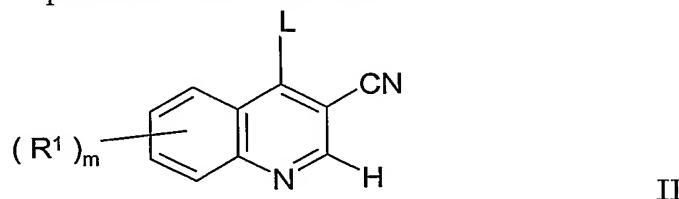
or a pharmaceutically-acceptable acid-addition salt thereof.

A quinoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, may be prepared by any process known to be applicable to the preparation of chemically-related compounds. Such processes, when used to prepare a quinoline derivative of the

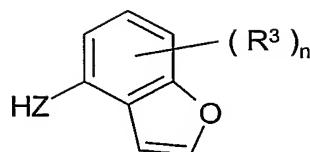
15 Formula I are provided as a further feature of the invention and are illustrated by the following representative process variants in which, unless otherwise stated, m, R¹, Z, n and R³ have any of the meanings defined hereinbefore. Necessary starting materials may be obtained by standard procedures of organic chemistry. The preparation of such starting materials is described in conjunction with the following representative process variants and within the

20 accompanying Examples. Alternatively necessary starting materials are obtainable by analogous procedures to those illustrated which are within the ordinary skill of an organic chemist.

(a) For the production of those compounds of the Formula I wherein Z is an O, S or N(R²) group, the reaction of a quinoline of the Formula II



25 wherein L is a displaceable group and m and R¹ have any of the meanings defined hereinbefore except that any functional group is protected if necessary, with a compound of the Formula III



III

wherein Z is O, S, or N(R²) and n, R³ and R² have any of the meanings defined hereinbefore except that any functional group is protected if necessary, whereafter any protecting group that is present is removed by conventional means.

5 The reaction may conveniently be carried out in the presence of a suitable acid or in the presence of a suitable base. A suitable acid is, for example, an inorganic acid such as, for example, hydrogen chloride or hydrogen bromide. A suitable base is, for example, an organic amine base such as, for example, pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, morpholine, N-methylmorpholine or diazabicyclo[5.4.0]undec-7-ene, or, for 10 example, an alkali or alkaline earth metal carbonate or hydroxide, for example sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide, or, for example, an alkali metal amide, for example sodium hexamethyldisilazane, or, for example, an alkali metal hydride, for example sodium hydride.

A suitable displaceable group L is, for example, a halogeno, alkoxy, aryloxy or 15 sulphonyloxy group, for example a chloro, bromo, methoxy, phenoxy, pentafluorophenoxy, methanesulphonyloxy or toluene-4-sulphonyloxy group. The reaction is conveniently carried out in the presence of a suitable inert solvent or diluent, for example an alcohol or ester such as methanol, ethanol, isopropanol or ethyl acetate, a halogenated solvent such as methylene chloride, chloroform or carbon tetrachloride, an ether such as tetrahydrofuran or 1,4-dioxan, 20 an aromatic solvent such as toluene, or a dipolar aprotic solvent such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one or dimethylsulphoxide. The reaction is conveniently carried out at a temperature in the range, for example, 0 to 250°C, preferably in the range 0 to 120°C.

Typically, the quinoline of the Formula II may be reacted with a compound of the 25 Formula III in the presence of an aprotic solvent such as N,N-dimethylformamide, conveniently in the presence of a base, for example potassium carbonate or sodium hexamethyldisilazane, and at a temperature in the range, for example, 0 to 150°C, preferably in the range, for example, 0 to 70°C.

The quinoline derivative of the Formula I may be obtained from this process in the 30 form of the free base or alternatively it may be obtained in the form of a salt with the acid of

the formula H-L wherein L has the meaning defined hereinbefore. When it is desired to obtain the free base from the salt, the salt may be treated with a suitable base, for example, an organic amine base such as, for example, pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, morpholine, N-methylmorpholine or 5 diazabicyclo[5.4.0]undec-7-ene, or, for example, an alkali or alkaline earth metal carbonate or hydroxide, for example sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide.

Protecting groups may in general be chosen from any of the groups described in the literature or known to the skilled chemist as appropriate for the protection of the group in 10 question and may be introduced by conventional methods. Protecting groups may be removed by any convenient method as described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with minimum disturbance of groups elsewhere in the molecule.

15 Specific examples of protecting groups are given below for the sake of convenience, in which "lower", as in, for example, lower alkyl, signifies that the group to which it is applied preferably has 1-4 carbon atoms. It will be understood that these examples are not exhaustive. Where specific examples of methods for the removal of protecting groups are given below these are similarly not exhaustive. The use of protecting groups and methods of deprotection 20 not specifically mentioned are, of course, within the scope of the invention.

A carboxy protecting group may be the residue of an ester-forming aliphatic or arylaliphatic alcohol or of an ester-forming silanol (the said alcohol or silanol preferably containing 1-20 carbon atoms). Examples of carboxy protecting groups include straight or branched chain (1-12C)alkyl groups (for example isopropyl, and tert-butyl); 25 lower alkoxy- lower alkyl groups (for example methoxymethyl, ethoxymethyl and isobutoxymethyl); lower acyloxy-lower alkyl groups, (for example acetoxyethyl, propionyloxymethyl, butyryloxymethyl and pivaloyloxymethyl); lower alkoxy carbonyloxy-lower alkyl groups (for example 1-methoxycarbonyloxyethyl and 1-ethoxycarbonyloxyethyl); aryl-lower alkyl groups (for example benzyl, 4-methoxybenzyl, 30 2-nitrobenzyl, 4-nitrobenzyl, benzhydryl and phthalidyl); tri(lower alkyl)silyl groups (for example trimethylsilyl and tert-butyldimethylsilyl); tri(lower alkyl)silyl-lower alkyl groups (for example trimethylsilylethyl); and (2-6C)alkenyl groups (for example allyl). Methods

particularly appropriate for the removal of carboxyl protecting groups include for example acid-, base-, metal- or enzymically-catalysed cleavage.

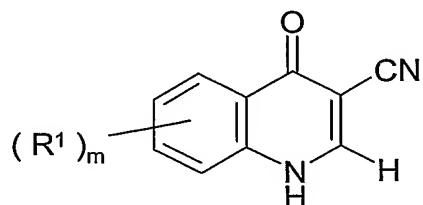
Examples of hydroxy protecting groups include lower alkyl groups (for example tert-butyl), lower alkenyl groups (for example allyl); lower alkanoyl groups (for example 5 acetyl); lower alkoxy carbonyl groups (for example tert-butoxycarbonyl); lower alkenyloxy carbonyl groups (for example allyloxy carbonyl); aryl-lower alkoxy carbonyl groups (for example benzyloxy carbonyl, 4-methoxybenzyloxy carbonyl, 2-nitrobenzyloxy carbonyl and 4-nitrobenzyloxy carbonyl); tri(lower alkyl)silyl (for example trimethylsilyl and tert-butyldimethylsilyl) and aryl-lower alkyl (for example benzyl) groups.

10 Examples of amino protecting groups include formyl, aryl-lower alkyl groups (for example benzyl and substituted benzyl, 4-methoxybenzyl, 2-nitrobenzyl and 2,4-dimethoxybenzyl, and triphenylmethyl); di-4-anisylmethyl and furylmethyl groups; lower alkoxy carbonyl (for example tert-butoxycarbonyl); lower alkenyloxy carbonyl (for example allyloxy carbonyl); aryl-lower alkoxy carbonyl groups (for example benzyloxy carbonyl, 15 4-methoxybenzyloxy carbonyl, 2-nitrobenzyloxy carbonyl and 4-nitrobenzyloxy carbonyl); trialkylsilyl (for example trimethylsilyl and tert-butyldimethylsilyl); alkylidene (for example methylidene) and benzylidene and substituted benzylidene groups.

Methods appropriate for removal of hydroxy and amino protecting groups include, for example, acid-, base-, metal- or enzymically-catalysed hydrolysis for groups such as 20 2-nitrobenzyloxy carbonyl, hydrogenation for groups such as benzyl and photolytically for groups such as 2-nitrobenzyloxy carbonyl.

The reader is referred to Advanced Organic Chemistry, 4th Edition, by J. March, published by John Wiley & Sons 1992, for general guidance on reaction conditions and reagents and to Protective Groups in Organic Synthesis, 2nd Edition, by T. Green *et al.*, also 25 published by John Wiley & Son, for general guidance on protecting groups.

Quinoline starting materials of the Formula II may be obtained by conventional procedures such as those disclosed in International Patent Applications WO 98/43960 and WO 00/68201. For example, a 1,4-dihydroquinolin-4-one of Formula IV



wherein m and R¹ have any of the meanings defined hereinbefore except that any functional group is protected if necessary, may be reacted with a halogenating agent such as thionyl chloride, phosphoryl chloride or a mixture of carbon tetrachloride and triphenylphosphine whereafter any protecting group that is present is removed by conventional means.

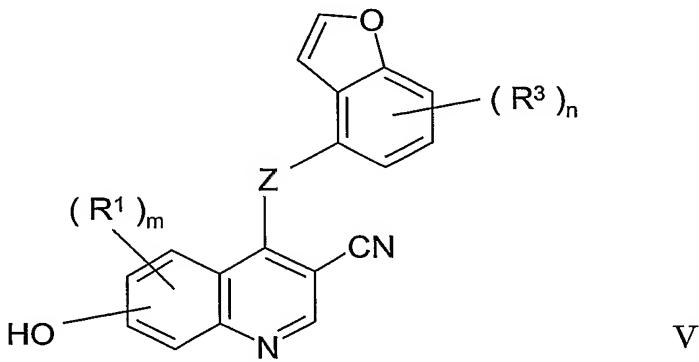
5 The 4-chloroquinoline so obtained may be converted, if required, into a 4-pentafluorophenoxyquinoline by reaction with pentafluorophenol in the presence of a suitable base such as potassium carbonate and in the presence of a suitable solvent such as N,N-dimethylformamide.

10 4-Aminobenzofuran starting materials (Formula III, for example when Z is NH) may be obtained by conventional procedures as illustrated in the Examples. Corresponding 4-hydroxybenzofuran and 4-mercaptopbenzofuran starting materials (Formula III, when Z is O or S respectively) may be obtained by conventional procedures.

(b) For the production of those compounds of the Formula I wherein at least one R¹ group is a group of the formula

15 Q^1-X^1-

wherein Q¹ is an aryl-(1-6C)alkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl-(1-6C)alkyl or heterocyclyl-(1-6C)alkyl group or an optionally substituted alkyl group and X¹ is an oxygen atom, the coupling, conveniently in the presence of a suitable dehydrating agent, of a quinoline of the Formula V



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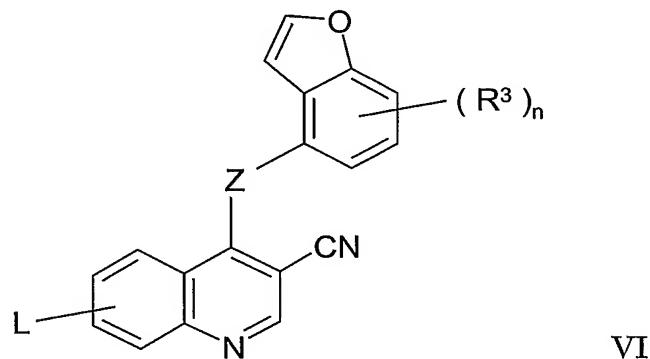
wherein m, R¹, Z, n and R³ have any of the meanings defined hereinbefore except that any functional group is protected if necessary, with an appropriate alcohol wherein any functional group is protected if necessary whereafter any protecting group that is present is removed by conventional means.

25 A suitable dehydrating agent is, for example, a carbodiimide reagent such as dicyclohexylcarbodiimide or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide or a mixture of

an azo compound such as diethyl or di-*tert*-butyl azodicarboxylate and a phosphine such as triphenylphosphine. The reaction is conveniently carried out in the presence of a suitable inert solvent or diluent, for example a halogenated solvent such as methylene chloride, chloroform or carbon tetrachloride and at a temperature in the range, for example, 10 to 150°C, preferably 5 at or near ambient temperature.

The reaction is conveniently carried out in the presence of a suitable inert solvent or diluent, for example a halogenated solvent such as methylene chloride, chloroform or carbon tetrachloride and at a temperature in the range, for example, 10 to 150°C, preferably at or near ambient temperature.

10 (c) For the production of those compounds of the Formula I wherein an R¹ group contains a (1-6C)alkoxy or substituted (1-6C)alkoxy group or a (1-6C)alkylamino or substituted (1-6C)alkylamino group, the reaction, conveniently in the presence of a suitable base as defined hereinbefore, of a quinoline derivative of the Formula VI



15 wherein L is a displaceable group as defined hereinbefore and Z, n and R³ have any of the meanings defined hereinbefore except that any functional group is protected if necessary, with an alcohol or amine as appropriate whereafter any protecting group that is present is removed by conventional means.

The reaction is conveniently carried out in the presence of a suitable inert diluent or 20 carrier as defined hereinbefore and at a temperature in the range 10 to 150°C, preferably at or near 50°C.

(d) For the production of those compounds of the Formula I wherein R¹ is an amino-substituted (1-6C)alkoxy group (such as 2-homopiperidin-1-ylethoxy or 25 3-dimethylaminopropoxy), the reaction of a compound of the Formula I wherein R¹ is a halogeno-substituted (1-6C)alkoxy group with a heterocyclyl compound or an appropriate amine.

The reaction is conveniently carried out in the presence of a suitable inert diluent or carrier as defined hereinbefore and at a temperature in the range 10 to 150°C, preferably at or near ambient temperature.

(e) For the production of those compounds of the Formula I wherein R¹ is a hydroxy group, the cleavage of a quinoline derivative of the Formula I wherein R¹ is a (1-6C)alkoxy or arylmethoxy group.

The cleavage reaction may conveniently be carried out by any of the many procedures known for such a transformation. The cleavage reaction of a compound of the Formula I wherein R¹ is a (1-6C)alkoxy group may be carried out, for example, by treatment of the quinoline derivative with an alkali metal (1-6C)alkylsulphide such as sodium ethanethiolate or, for example, by treatment with an alkali metal diarylphosphide such as lithium diphenylphosphide. Alternatively the cleavage reaction may conveniently be carried out, for example, by treatment of the quinoline derivative with a boron or aluminium trihalide such as boron tribromide. The cleavage reaction of a compound of the Formula I wherein R¹ is a arylmethoxy group may be carried out, for example, by hydrogenation of the quinoline derivative in the presence of a suitable metallic catalyst such as palladium or by reaction with an organic or inorganic acid, for example trifluoroacetic acid. Such reactions are preferably carried out in the presence of a suitable inert solvent or diluent as defined hereinbefore and at a temperature in the range, for example, 10 to 150°C, preferably at or near ambient temperature.

(f) For the production of those compounds of the Formula I wherein an R¹ group contains a primary or secondary amino group, the cleavage of the corresponding compound of the Formula I wherein the R¹ group contains a protected primary or secondary amino group.

Suitable protecting groups for an amino group are, for example, any of the protecting groups disclosed hereinbefore for an amino group. Suitable methods for the cleavage of such amino protecting groups are also disclosed hereinbefore. In particular, a suitable protecting group is a lower alkoxy carbonyl group such as a tert-butoxycarbonyl group which may be cleaved under conventional reaction conditions such as under acid-catalysed hydrolysis, for example in the presence of trifluoroacetic acid.

(g) For the production of those compounds of the Formula I wherein an R¹ group contains a (1-6C)alkoxy or substituted (1-6C)alkoxy group or a (1-6C)alkylamino or substituted (1-6C)alkylamino group, the alkylation, conveniently in the presence of a suitable base as defined hereinbefore, of a quinoline derivative of the formula I wherein the R¹ group contains

a hydroxy group or a primary or secondary amino group as appropriate.

A suitable alkylating agent is, for example, any agent known in the art for the alkylation of hydroxy to alkoxy or substituted alkoxy, or for the alkylation of amino to alkylamino or substituted alkylamino, for example an alkyl or substituted alkyl halide, for example a (1-6C)alkyl chloride, bromide or iodide or a substituted (1-6C)alkyl chloride, bromide or iodide, conveniently in the presence of a suitable base as defined hereinbefore, in a suitable inert solvent or diluent as defined hereinbefore and at a temperature in the range, for example, 10 to 140°C, conveniently at or near ambient temperature.

Conveniently for the production of those compounds of the Formula I wherein R¹ contains a (1-6C)alkylamino or substituted (1-6C)alkylamino group, a reductive amination reaction may be employed. For example, for the production of those compounds of the Formula I wherein R¹ contains a N-methyl group, the corresponding compound containing a N-H group may be reacted with formaldehyde in the presence of a suitable reducing agent. A suitable reducing agent is, for example, a hydride reducing agent, for example an alkali metal aluminium hydride such as lithium aluminium hydride or, preferably, an alkali metal borohydride such as sodium borohydride, sodium cyanoborohydride, sodium triethylborohydride, sodium trimethoxyborohydride and sodium triacetoxyborohydride. The reaction is conveniently performed in a suitable inert solvent or diluent, for example tetrahydrofuran and diethyl ether for the more powerful reducing agents such as lithium aluminium hydride, and, for example, methylene chloride or a protic solvent such as methanol and ethanol for the less powerful reducing agents such as sodium triacetoxyborohydride and sodium cyanoborohydride. The reaction is performed at a temperature in the range, for example, 10 to 80°C, conveniently at or near ambient temperature.

(h) For the production of those compounds of the Formula I wherein R¹ is an amino-hydroxy-disubstituted (1-6C)alkoxy group (such as 2-hydroxy-3-pyrrolidin-1-ylpropoxy or 3-[N-allyl-N-methylamino]-2-hydroxypropoxy), the reaction of a compound of the Formula I wherein the R¹ group contains an epoxy-substituted (1-6C)alkoxy group with a heterocyclyl compound or an appropriate amine.

The reaction is conveniently carried out in the presence of a suitable inert diluent or carrier as defined hereinbefore and at a temperature in the range 10 to 150°C, preferably at or near ambient temperature.

(i) For the production of those compounds of the Formula I wherein an R¹ group contains a hydroxy group, the cleavage of the corresponding compound of the Formula I wherein the R¹ group contains a protected hydroxy group.

Suitable protecting groups for a hydroxy group are, for example, any of the protecting groups disclosed hereinbefore. Suitable methods for the cleavage of such hydroxy protecting groups are also disclosed hereinbefore. In particular, a suitable protecting group is a lower alkanoyl group such as an acetyl group which may be cleaved under conventional reaction conditions such as under base-catalysed conditions, for example in the presence of ammonia.

(j) For the production of those compounds of the Formula I wherein Z is a SO or SO₂ group, the oxidation of a compound of Formula I wherein Z is a S group.

Conventional oxidation reagents and reaction conditions for such partial or complete oxidation of a sulphur atom are well known to the organic chemist.

(k) The conversion of a compound of the Formula I wherein an R¹ or R³ substituent is a halogeno group into a further compound of the Formula I wherein the R¹ or R³ substituent is, for example, a cyano, ethynyl or phenyl group.

For example, a compound of the Formula I wherein an R¹ or R³ substituent is a halogeno group may be reacted with a metal cyanide to form a compound of the Formula I wherein an R¹ or R³ substituent is a cyano group. Conveniently, the reaction may be carried out in the presence of a suitable catalyst. A suitable metal cyanide is, for example, a heavy metal cyanide such as zinc cyanide. A suitable catalyst is, for example, an organometallic reagent, for example an organoiron compound such as diphenylphosphinoferrocene. The conversion reaction is conveniently carried out in the presence of a suitable inert diluent or carrier as defined hereinbefore and at a temperature in the range 10 to 150°C, preferably at or near 100°C.

For example, a compound of the Formula I wherein an R¹ or R³ substituent is a halogeno group may be reacted with a (2-6C)alkyne to form a compound of the Formula I wherein an R¹ or R³ substituent is a (2-6C)alkynyl group such as an ethynyl group. The reaction may conveniently be carried out in the presence of a suitable base as defined hereinbefore and in the presence of a suitable catalyst. For this conversion, a suitable catalyst is, for example, an organometallic reagent, for example an organopalladium compound such as tetrakis(triphenylphosphine)palladium(0). The conversion reaction is conveniently carried out in the presence of a suitable inert diluent or carrier as defined hereinbefore and at a temperature in the range 10 to 150°C, preferably at or near 60°C.

For example, a compound of the Formula I wherein an R¹ or R³ substituent is a halogeno group may be reacted with an arylboron reagent to form a compound of the Formula I wherein an R¹ or R³ substituent is an aryl group such as a phenyl group. A suitable arylboron reagent is, for example, an arylboronic acid. The reaction may conveniently be 5 carried out in the presence of a suitable catalyst, for example, an organopalladium compound such as tetrakis(triphenylphosphine)palladium(0). The conversion reaction is conveniently carried out in the presence of a suitable inert diluent or carrier as defined hereinbefore and at a temperature in the range 10 to 150°C, preferably at or near 80°C.

When a pharmaceutically-acceptable salt of a quinoline derivative of the Formula I is 10 required, for example an acid-addition salt, it may be obtained by, for example, reaction of said quinoline derivative with a suitable acid using a conventional procedure.

Biological Assays

The following assays can be used to measure the effects of the compounds of the present invention as c-Src tyrosine kinase inhibitors, as inhibitors in vitro of the proliferation 15 of c-Src transfected fibroblast cells, as inhibitors in vitro of the migration of A549 human lung tumour cells and as inhibitors in vivo of the growth in nude mice of xenografts of A549 tissue.

(a) In Vitro Enzyme Assay

The ability of test compounds to inhibit the phosphorylation of a tyrosine containing polypeptide substrate by the enzyme c-Src kinase was assessed using a conventional Elisa 20 assay.

A substrate solution [100µl of a 20µg/ml solution of the polyamino acid Poly(Glu, Tyr) 4:1 (Sigma Catalogue No. P0275) in phosphate buffered saline (PBS) containing 0.2mg/ml of sodium azide] was added to each well of a number of Nunc 96-well 25 immunoplates (Catalogue No. 439454) and the plates were sealed and stored at 4°C for 16 hours. The excess of substrate solution was discarded, and aliquots of Bovine Serum Albumin (BSA; 150µl of a 5% solution in PBS) were transferred into each substrate-coated assay well and incubated for 1 hour at ambient temperature to block non specific binding. The assay plate wells were washed in turn with PBS containing 0.05% v/v Tween 20 (PBST) and with Hepes pH7.4 buffer (50mM, 300µl/well) before being blotted dry.

30 Each test compound was dissolved in dimethyl sulphoxide and diluted with distilled water to give a series of dilutions (from 100µM to 0.001µM). Portions (25µl) of each dilution of test compound were transferred to wells in the washed assay plates. "Total" control wells

contained diluted DMSO instead of compound. Aliquots (25 μ l) of an aqueous magnesium chloride solution (80mM) containing adenosine-5'-triphosphate (ATP; 40 μ M) was added to all test wells except the "blank" control wells which contained magnesium chloride without ATP.

5 Active human c-Src kinase (recombinant enzyme expressed in Sf9 insect cells; obtained from Upstate Biotechnology Inc. product 14-117) was diluted immediately prior to use by a factor of 1:10,000 with an enzyme diluent which comprised 100mM Hepes pH7.4 buffer, 0.2mM sodium orthovanadate, 2mM dithiothreitol and 0.02% BSA. To start the reactions, aliquots (50 μ l) of freshly diluted enzyme were added to each well and the plates
10 were incubated at ambient temperature for 20 minutes. The supernatant liquid in each well was discarded and the wells were washed twice with PBST. Mouse IgG anti-phosphotyrosine antibody (Upstate Biotechnology Inc. product 05-321; 100 μ l) was diluted by a factor of 1:6000 with PBST containing 0.5% w/v BSA and added to each well. The plates were
15 incubated for 1 hour at ambient temperature. The supernatant liquid was discarded and each well was washed with PBST (x4). Horse radish peroxidase (HRP)-linked sheep anti-mouse Ig antibody (Amersham Catalogue No. NXA 931; 100 μ l) was diluted by a factor of 1:500 with PBST containing 0.5% w/v BSA and added to each well. The plates were incubated for 1 hour at ambient temperature. The supernatant liquid was discarded and the wells were washed with PBST (x4).

20 A PCSB capsule (Sigma Catalogue No. P4922) was dissolved in distilled water (100ml) to provide phosphate-citrate pH5 buffer (50mM) containing 0.03% sodium perborate. An aliquot (50ml) of this buffer was mixed with a 50mg tablet of 2,2'-azinobis(3-ethylbenzothiazoline-6-sulphonic acid) (ABTS; Boehringer Catalogue No. 1204 521). Aliquots (100 μ l) of the resultant solution were added to each well. The plates
25 were incubated for 20 to 60 minutes at ambient temperature until the optical density value of the "total" control wells, measured at 405nm using a plate reading spectrophotometer, was approximately 1.0. "Blank" (no ATP) and "total" (no compound) control values were used to determine the dilution range of test compound which gave 50% inhibition of enzyme activity.

(b) In Vitro c-Src transfected NIH 3T3 (c-src 3T3) Fibroblast Proliferation Assay

30 This assay determined the ability of a test compound to inhibit the proliferation of National Institute of Health (NIH) mouse 3T3 fibroblast cells that had been stably-transfected with an activating mutant (Y530F) of human c-Src.

Using a similar procedure to that described by Shalloway *et al.*, Cell, 1987, 49, 65-73, NIH 3T3 cells were transfected with an activating mutant (Y530F) of human c-Src. The resultant c-Src 3T3 cells were typically seeded at 1.5×10^4 cells per well into 96-well tissue-culture-treated clear assay plates (Costar) each containing an assay medium comprising

5 Dulbecco's modified Eagle's medium (DMEM; Sigma) plus 0.5% foetal calf serum (FCS), 2mM glutamine, 100 units/ml penicillin and 0.1mg/ml streptomycin in 0.9% aqueous sodium chloride solution. The plates were incubated overnight at 37°C in a humidified (7.5% CO₂ : 95% air) incubator.

Test compounds were solubilised in DMSO to form a 10mM stock solution. Aliquots 10 of the stock solution were diluted with the DMEM medium described above and added to appropriate wells. Serial dilutions were made to give a range of test concentrations. Control wells to which test compound was not added were included on each plate. The plates were incubated overnight at 37°C in a humidified (7.5% CO₂ : 95% air) incubator.

BrdU labelling reagent (Boehringer Mannheim Catalogue No. 647 229) was diluted by 15 a factor of 1:100 in DMEM medium containing 0.5% FCS and aliquots (20μl) were added to each well to give a final concentration of 10μM. The plates were incubated at 37°C for 2 hours. The medium was decanted. A denaturing solution (FixDenat solution, Boehringer Mannheim Catalogue No. 647 229; 50μl) was added to each well and the plates were placed on a plate shaker at ambient temperature for 45 minutes. The supernatant was decanted and 20 the wells were washed with PBS (200μl per well). Anti-BrdU-Peroxidase solution (Boehringer Mannheim Catalogue No. 647 229) was diluted by a factor of 1:100 in PBS containing 1% BSA and 0.025% dried skimmed milk (Marvel (registered trade mark), Premier Beverages, Stafford, GB) and an aliquot (100μl) of the resultant solution was added to each well. The plates were placed on a plate shaker at ambient temperature for 90 minutes. The 25 wells were washed with PBS (x5) to ensure removal of non-bound antibody conjugate. The plates were blotted dry and tetramethylbenzidine substrate solution (Boehringer Mannheim Catalogue No. 647 229; 100μl) was added to each well. The plates were gently agitated on a plate shaker while the colour developed during a 10 to 20 minute period. The absorbance of the wells was measured at 690nm. The extent of inhibition of cellular proliferation at a range 30 of concentrations of each test compound was determined and an anti-proliferative IC₅₀ value was derived.

(c) In Vitro Microdroplet Migration Assay

This assay determines the ability of a test compound to inhibit the migration of adherent mammalian cell lines, for example the human tumour cell line A549.

RPMI medium (Sigma) containing 10% FCS, 1% L-glutamine and 0.3% agarose (Difco Catalogue No. 0142-01) was warmed to 37°C in a water bath. A stock 2% aqueous agar solution was autoclaved and stored at 42°C. An aliquot (1.5 ml) of the agar solution was added to RPMI medium (10 ml) immediately prior to its use. A549 cells (Accession No. ATCC CCL185) were suspended at a concentration of 2×10^7 cells/ml in the medium and maintained at a temperature of 37°C.

10 A droplet (2 μ l) of the cell/agarose mixture was transferred by pipette into the centre of each well of a number of 96-well, flat bottomed non-tissue-culture-treated microtitre plate (Bibby Sterilin Catalogue No. 642000). The plates were placed briefly on ice to speed the gelling of the agarose-containing droplets. Aliquots (90 μ l) of medium which had been cooled to 4°C were transferred into each well, taking care not to disturb the microdroplets. Test 15 compounds were diluted from a 10mM stock solution in DMSO using RPMI medium as described above. Aliquots (10 μ l) of the diluted test compounds were transferred to the wells, again taking care not to disturb the microdroplets. The plates were incubated at 37°C in a humidified (7.5% CO₂ : 95% air) incubator for about 48 hours.

20 Migration was assessed visually and the distance of migration was measured back to the edge of the agar droplet. A migratory inhibitory IC₅₀ was derived by plotting the mean migration measurement against test compound concentration.

(d) In Vivo A549 Xenograft Growth Assay

This test measures the ability of compounds to inhibit the growth of the A549 human carcinoma grown as a tumour in athymic nude mice (Alderley Park nu/nu strain). A total of 25 about 5×10^6 A549 cells in matrigel (Beckton Dickinson Catalogue No. 40234) were injected subcutaneously into the left flank of each test mouse and the resultant tumours were allowed to grow for about 14 days. Tumour size was measured twice weekly using callipers and a theoretical volume was calculated. Animals were selected to provide control and treatment groups of approximately equal average tumour volume. Test compounds were prepared as a 30 ball-milled suspension in 1% polysorbate vehicle and dosed orally once daily for a period of about 28 days. The effect on tumour growth was assessed.

Although the pharmacological properties of the compounds of the Formula I vary with structural change as expected, in general activity possessed by compounds of the Formula I, may be demonstrated at the following concentrations or doses in one or more of the above tests (a), (b), (c) and (d):-

5 Test (a):- IC_{50} in the range, for example, 0.001 - 10 μM ;
Test (b):- IC_{50} in the range, for example, 0.01 - 20 μM ;
Test (c):- activity in the range, for example, 0.1-25 μM ;
Test (d):- activity in the range, for example, 1-200 mg/kg/day;.

No physiologically-unacceptable toxicity was observed in Test (d) at the effective dose
10 for compounds tested of the present invention. Accordingly no untoward toxicological effects
are expected when a compound of Formula I, or a pharmaceutically-acceptable salt thereof, as
defined hereinbefore is administered at the dosage ranges defined hereinafter.

According to a further aspect of the invention there is provided a pharmaceutical
composition which comprises a quinoline derivative of the Formula I, or a pharmaceutically-
15 acceptable salt thereof, as defined hereinbefore in association with a pharmaceutically-
acceptable diluent or carrier.

The compositions of the invention may be in a form suitable for oral use (for example
as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible
powders or granules, syrups or elixirs), for topical use (for example as creams, ointments,
20 gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for
example as a finely divided powder or a liquid aerosol), for administration by insufflation (for
example as a finely divided powder) or for parenteral administration (for example as a sterile
aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing
or as a suppository for rectal dosing).

25 The compositions of the invention may be obtained by conventional procedures using
conventional pharmaceutical excipients, well known in the art. Thus, compositions intended
for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or
preservative agents.

The amount of active ingredient that is combined with one or more excipients to
30 produce a single dosage form will necessarily vary depending upon the host treated and the
particular route of administration. For example, a formulation intended for oral
administration to humans will generally contain, for example, from 0.5 mg to 0.5 g of active
agent (more suitably from 0.5 to 100 mg, for example from 1 to 30 mg) compounded with an

appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition.

The size of the dose for therapeutic or prophylactic purposes of a compound of the Formula I will naturally vary according to the nature and severity of the conditions, the age 5 and sex of the animal or patient and the route of administration, according to well known principles of medicine.

In using a compound of the Formula I for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 0.1 mg/kg to 75 mg/kg body weight is received, given if required in divided doses. In general lower doses 10 will be administered when a parenteral route is employed. Thus, for example, for intravenous administration, a dose in the range, for example, 0.1 mg/kg to 30 mg/kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for example, 0.05 mg/kg to 25 mg/kg body weight will be used. Oral administration is however preferred, particularly in tablet form. Typically, unit dosage forms will contain about 0.5 mg 15 to 0.5 g of a compound of this invention.

According to a further aspect of the invention there is provided a quinoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore for use in a method of treatment of the human or animal body by therapy.

As stated above, it is known that the predominant role of c-Src non-receptor tyrosine 20 kinase is to regulate cell motility which is necessarily required for a localised tumour to progress through the stages of dissemination into the blood stream, invasion of other tissues and initiation of metastatic tumour growth. We have found that the quinoline derivatives of the present invention possess potent anti-tumour activity which it is believed is obtained by way of inhibition of one or more of the non-receptor tyrosine-specific protein kinases such as 25 c-Src kinase that are involved in the signal transduction steps which lead to the invasiveness and migratory ability of metastasising tumour cells.

Accordingly the quinoline derivatives of the present invention are of value as anti-tumour agents, in particular as selective inhibitors of the motility, dissemination and invasiveness of mammalian cancer cells leading to inhibition of metastatic tumour growth. 30 Particularly, the quinoline derivatives of the present invention are of value as anti-invasive agents in the containment and/or treatment of solid tumour disease. Particularly, the compounds of the present invention are expected to be useful in the prevention or treatment of those tumours which are sensitive to inhibition of one or more of the multiple non-receptor

tyrosine kinases such as c-Src kinase that are involved in the signal transduction steps which lead to the invasiveness and migratory ability of metastasising tumour cells. Further, the compounds of the present invention are expected to be useful in the prevention or treatment of those tumours which are mediated alone or in part by inhibition of the enzyme c-Src, *i.e.* the 5 compounds may be used to produce a c-Src enzyme inhibitory effect in a warm-blooded animal in need of such treatment. Specifically, the compounds of the present invention are expected to be useful in the prevention or treatment of solid tumour disease.

Thus according to this aspect of the invention there is provided a quinoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore for use 10 as an anti-invasive agent in the containment and/or treatment of solid tumour disease.

According to a further feature of this aspect of the invention there is provided the use of a quinoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use as an anti-invasive agent in the containment and/or treatment of solid tumour disease.

15 According to a further feature of this aspect of the invention there is provided a method for producing an anti-invasive effect by the containment and/or treatment of solid tumour disease in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a quinoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

20 According to a further aspect of the invention there is provided the use of a quinoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the prevention or treatment of solid tumour disease in a warm-blooded animal such as man.

According to a further feature of this aspect of the invention there is provided a 25 method for the prevention or treatment of solid tumour disease in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a quinoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

According to a further aspect of the invention there is provided the use of a quinoline 30 derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the prevention or treatment of those tumours which are sensitive to inhibition of non-receptor tyrosine kinases such as c-Src

kinase that are involved in the signal transduction steps which lead to the invasiveness and migratory ability of metastasising tumour cells.

According to a further feature of this aspect of the invention there is provided a method for the prevention or treatment of those tumours which are sensitive to inhibition of 5 non-receptor tyrosine kinases such as c-Src kinase that are involved in the signal transduction steps which lead to the invasiveness and migratory ability of metastasising tumour cells which comprises administering to said animal an effective amount of a quinoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

According to a further aspect of the invention there is provided the use of a quinoline 10 derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in providing a c-Src kinase inhibitory effect.

According to a further feature of this aspect of the invention there is provided a method for providing a c-Src kinase inhibitory effect which comprises administering to said 15 animal an effective amount of a quinoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

The anti-invasive treatment defined hereinbefore may be applied as a sole therapy or may involve, in addition to the quinoline derivative of the invention, conventional surgery or radiotherapy or chemotherapy. Such chemotherapy may include one or more of the following 20 categories of anti-tumour agents :-

- (i) other anti-invasion agents (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function);
- (ii) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as alkylating agents (for example cis-platin, carboplatin, cyclophosphamide, 25 nitrogen mustard, melphalan, chlorambucil, busulphan and nitrosoureas); antimetabolites (for example antifolates such as fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside and hydroxyurea, or, for example, one of the preferred antimetabolites disclosed in European Patent Application No. 562734 such as (2S)-2-{ α -fluoro-p-[N-{2,7-dimethyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl}-
- 30 N -(prop-2-ynyl)amino]benzamido}-4-(tetrazol-5-yl)butyric acid); antitumour antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol

and taxotere); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan and camptothecin);

(iii) cytostatic agents such as antioestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene and idoxifene), antiandrogens (for example bicalutamide, flutamide, 5 nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprorelin and buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrozole, vorazole and exemestane) and inhibitors of 5 α -reductase such as finasteride;

(iv) inhibitors of growth factor function, for example such inhibitors include growth factor 10 antibodies, growth factor receptor antibodies, tyrosine kinase inhibitors and serine/threonine kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example the EGFR tyrosine kinase inhibitors N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (ZD1839), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (CP 358774) and 6-acrylamido-N-(3-chloro-15 4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (CI 1033)), for example inhibitors of the platelet-derived growth factor family and for example inhibitors of the hepatocyte growth factor family; and

(v) antiangiogenic agents such as those which inhibit vascular endothelial growth factor 20 such as the compounds disclosed in International Patent Applications WO 97/22596, WO 97/30035, WO 97/32856 and WO 98/13354 and those that work by other mechanisms (for example linomide, inhibitors of integrin $\alpha v\beta 3$ function and angiostatin).

Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment. Such combination products employ the compounds of this invention within the dosage range described hereinbefore and 25 the other pharmaceutically-active agent within its approved dosage range.

According to this aspect of the invention there is provided a pharmaceutical product comprising a quinoline derivative of the formula I as defined hereinbefore and an additional anti-tumour agent as defined hereinbefore for the conjoint treatment of cancer.

Although the compounds of the Formula I are primarily of value as therapeutic agents 30 for use in warm-blooded animals (including man), they are also useful whenever it is required to inhibit the effects of c-Src. Thus, they are useful as pharmacological standards for use in the development of new biological tests and in the search for new pharmacological agents.

The invention will now be illustrated in the following Examples in which, generally :

(i) operations were carried out at ambient temperature, *i.e.* in the range 17 to 25°C and under an atmosphere of an inert gas such as argon unless otherwise stated;

5 (ii) evaporation were carried out by rotary evaporation *in vacuo* and work-up procedures were carried out after removal of residual solids by filtration;

(iii) column chromatography (by the flash procedure) and medium pressure liquid chromatography (MPLC) were performed on Merck Kieselgel silica (Art. 9385) or Merck Lichroprep RP-18 (Art. 9303) reversed-phase silica obtained from E. Merck, Darmstadt, Germany or high pressure liquid chromatography (HPLC) was performed on C18 reverse 10 phase silica, for example on a Dynamax C-18 60Å preparative reversed-phase column;

(iv) yields, where present, are not necessarily the maximum attainable;

(v) in general, the end-products of the Formula I have satisfactory microanalyses and their structures were confirmed by nuclear magnetic resonance (NMR) and/or mass spectral techniques; fast-atom bombardment (FAB) mass spectral data were obtained using a Platform 15 spectrometer and, where appropriate, either positive ion data or negative ion data were collected; NMR chemical shift values were measured on the delta scale [proton magnetic resonance spectra were determined using a Jeol JNM EX 400 spectrometer operating at a field strength of 400MHz, Varian Gemini 2000 spectrometer operating at a field strength of 300MHz or a Bruker AM300 spectrometer operating at a field strength of 300MHz]; the 20 following abbreviations have been used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad;

(vi) intermediates were not generally fully characterised and purity was assessed by thin layer chromatographic, HPLC, infra-red (IR) and/or NMR analysis;

(vii) melting points are uncorrected and were determined using a Mettler SP62 25 automatic melting point apparatus or an oil-bath apparatus; melting points for the end-products of the Formula I were determined after crystallisation from a conventional organic solvent such as ethanol, methanol, acetone, ether or hexane, alone or in admixture;

(viii) where certain compounds were obtained as an acid-addition salt, for example a mono hydrochloride salt or a dihydrochloride salt, the stoichiometry of the salt was based on 30 the number and nature of the basic groups in the compound, the exact stoichiometry of the salt was generally not determined, for example by means of elemental analysis data;

(ix) the following abbreviations have been used:-

- 62 -

DMF	<u>N,N</u> -dimethylformamide
DMSO	dimethylsulphoxide
THF	tetrahydrofuran

Example 1**4-benzofuran-4-ylamino-3-cyano-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinoline dihydrochloride salt**

Sodium hexamethyldisilazane (1M solution in THF; 0.9 ml) was added to a solution of 5 4-aminobenzofuran (0.12 g) in DMF (10 ml) that had been cooled to 0°C and the mixture was stirred for 5 minutes. A solution of 4-chloro-3-cyano-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinoline (0.17 g) in DMF (2 ml) was added and the resultant mixture was stirred at ambient temperature for 24 hours. The reaction mixture was evaporated and the residue was partitioned between ethyl acetate and water. The organic phase was washed with 10 water and with brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and a saturated methanolic ammonia solution as eluent. The material so obtained was dissolved in diethyl ether and a solution of hydrogen chloride in diethyl ether (1M, 2 ml) was added. The resultant solid was washed with diethyl ether and dried. There was thus 15 obtained the title compound (0.105 g); NMR Spectrum: (DMSO_d₆ and CD₃CO₂D) 2.32 (m, 2H), 2.85 (s, 3H), 3.27–3.85 (m, 10H), 4.0 (s, 3H), 4.33 (m, 2H), 7.07 (d, 1H), 7.35 (t, 1H), 7.43 (d, 1H), 7.51 (s, 1H), 7.72 (d, 1H), 7.96 (d, 1H), 8.22 (s, 1H), 8.92 (s, 1H); Mass Spectrum : M+H⁺ 472.

The 4-aminobenzofuran used as a starting material was prepared as follows :-
20 Allyl bromide (12.5 ml) and sodium iodide (1 g) were added in turn to a stirred mixture of methyl 3-hydroxybenzoate (20 g), potassium carbonate (22 g) and acetone (200 ml) and the resultant mixture was stirred at ambient temperature for 16 hours. The mixture was filtered and the solvent was evaporated. The residue was partitioned between methylene chloride and water. The organic phase was dried over magnesium sulphate and evaporated 25 and the residue was purified by column chromatography using increasingly polar mixtures of petroleum ether (b.p. 60-80°C) and ethyl acetate as eluent. There was thus obtained methyl 3-allyloxybenzoate as an oil (21.8 g); NMR Spectrum: (DMSO_d₆) 3.85 (s, 3H), 4.65 (d, 2H), 5.30 (m, 1H), 5.45 (m, 1H), 6.05 (m, 1H), 7.25 (m, 1H), 7.45 (m, 2H), 7.55 (d, 1H).

The methyl 3-allyloxybenzoate so obtained was heated to 200°C for 0.7 hours and then 30 to 230°C for 1 hour. The reaction product, comprising a mixture of methyl 2-allyl-3-hydroxybenzoate and methyl 4-allyl-3-hydroxybenzoate, was cooled to ambient temperature and partitioned between diethyl ether and 1N aqueous potassium hydroxide solution. The aqueous phase was allowed to stand for 30 minutes whereupon the methyl 4-allyl-

3-hydroxybenzoate was hydrolysed to 4-allyl-3-hydroxybenzoic acid. The aqueous phase was then acidified to pH1 by the addition of 6N aqueous hydrochloric acid and extracted with diethyl ether. The organic extract was washed with 10% aqueous potassium carbonate solution, dried over magnesium sulphate and evaporated. There was thus obtained methyl 5 2-allyl-3-hydroxybenzoate (10.7 g) as an oil; Mass Spectrum: M+H⁺ 192.

Using analogous procedures to those described in J. Med. Chem., 1995, 38, 3102-3103, methyl 2-allyl-3-hydroxybenzoate was converted in three steps via methyl 2-hydroxy-2,3-dihydrobenzofuran-4-carboxylate and methyl benzofuran-4-carboxylate into benzofuran-4-carboxylic acid.

10 A mixture of benzofuran-4-carboxylic acid (0.5 g), diphenylphosphoryl azide (1.2 ml), triethylamine (0.79 ml) and tert-butanol (1.5 ml) were stirred and heated to reflux for 18 hours. The mixture was cooled to ambient temperature and partitioned between ethyl acetate and water. The organic phase was washed in turn with water and brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography 15 using methylene chloride as eluent. There was thus obtained tert-butyl benzofuran-4-carbamate (0.8 g) as an oil; Mass Spectrum: M+Na⁺ 256.

20 Trifluoroacetic acid (2.5 ml) was added to a solution of tert-butyl benzofuran-4-carbamate (0.65 g) and methylene chloride (20 ml) which had been cooled to 0°C and the mixture was stirred for 1hour. The mixture was allowed to warm to ambient temperature and stirring was continued for 1.5 hours. The mixture was evaporated and the residue was 25 partitioned between ethyl acetate and water. The organic phase was dried over magnesium sulphate and evaporated. The resultant oil was purified by column chromatography using a 4:1 mixture of methylene chloride and petroleum ether (b.p. 60-80°C) as eluent. There was thus obtained 4-aminobenzofuran (0.35 g); NMR Spectrum: (DMSO_d₆) 5.5 (br s, 2H), 6.35 (d, 1H), 6.7 (d, 1H), 6.95 (d, 1H), 7.0 (d, 1H), 7.7 (d, 1H); Mass Spectrum: M+H⁺ 133.

The 4-chloro-3-cyano-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinoline used as a starting material was prepared as follows :-

30 A mixture of 3-bromopropanol (20 ml), N-methylpiperazine (29 ml), potassium carbonate (83 g) and ethanol (200 ml) was stirred and heated to reflux for 20 hours. The mixture was cooled to ambient temperature and filtered. The filtrate was evaporated and the residue was triturated under diethyl ether. The resultant mixture was filtered and the filtrate was evaporated. The residue was purified by distillation at about 60-70°C under about

0.2 mm Hg to give 1-(3-hydroxypropyl)-4-methylpiperazine (17 g); NMR Spectrum: (CDCl₃) 1.72 (m, 2H), 2.3 (s, 3H), 2.2-2.8 (m, 8H), 2.6 (t, 2H), 3.8 (t, 2H), 5.3 (br s, 1H).

Diethyl azodicarboxylate (0.25 g) was added dropwise to a suspension of 4-chloro-3-cyano-7-hydroxy-6-methoxyquinoline (0.2 g; , prepared as described in International Patent Application WO 00/68201, disclosed as compound (7) within Preparation 1 therein), 1-(3-hydroxypropyl)-4-methylpiperazine (0.202 g), triphenylphosphine (0.447 g) and methylene chloride (5 ml) and the mixture was stirred at ambient temperature for 2 hours. The resultant mixture was evaporated and the residue was purified by column chromatography on silica using initially increasingly polar mixtures of methylene chloride and ethyl acetate followed by increasingly polar mixtures of methylene chloride, ethyl acetate and a saturated methanolic ammonia solution as eluent. The material so obtained was triturated under diethyl ether. The resultant solid was isolated and dried under vacuum to give the required starting material (0.15 g); NMR Spectrum: (DMSO_d₆ and CF₃CO₂D) 1.95-2.05 (m, 2H), 2.2 (s, 3H), 2.25-2.5 (m, 10H), 4.05 (s, 3H), 4.3 (m, 2H), 7.45 (s, 1H), 7.58 (s, 1H), 9.0 (s, 1H); Mass Spectrum: M+H⁺ 375 and 377.

Example 2

Pharmaceutical compositions

The following illustrate representative pharmaceutical dosage forms of the invention as defined herein (the active ingredient being termed “Compound X”), for therapeutic or prophylactic use in humans:

		mg/tablet
	(a) Tablet I	
	Compound X.....	100
25	Lactose Ph.Eur.....	182.75
	Croscarmellose sodium.....	12.0
	Maize starch paste (5% w/v paste).....	2.25
	Magnesium stearate.....	3.0
	(b) Tablet II	mg/tablet
30	Compound X.....	50
	Lactose Ph.Eur.....	223.75
	Croscarmellose sodium.....	6.0

5	Maize starch.....	15.0
	Polyvinylpyrrolidone (5% w/v paste).....	2.25
	Magnesium stearate.....	3.0
10	Tablet III	mg/tablet
	Compound X.....	1.0
	Lactose Ph.Eur.....	93.25
	Croscarmellose sodium.....	4.0
	Maize starch paste (5% w/v paste).....	0.75
15	Magnesium stearate.....	1.0
	(d) Capsule	mg/capsule
	Compound X.....	10
	Lactose Ph.Eur.....	488.5
20	Magnesium.....	1.5
	(e) Injection I	(50 mg/ml)
	Compound X.....	5.0% w/v
	1M Sodium hydroxide solution.....	15.0% v/v
25	0.1M Hydrochloric acid (to adjust pH to 7.6)	
	Polyethylene glycol 400.....	4.5% w/v
	Water for injection to 100%	
	(f) Injection II	(10 mg/ml)
30	Compound X.....	1.0% w/v
	Sodium phosphate BP.....	3.6% w/v
	0.1M Sodium hydroxide solution.....	15.0% v/v
	Water for injection to 100%	
	(g) Injection III	(1mg/ml, buffered to pH6)
	Compound X.....	0.1% w/v
	Sodium phosphate BP.....	2.26% w/v

Citric acid.....	0.38% w/v
Polyethylene glycol 400.....	3.5% w/v
Water for injection to 100%	

5	(h) Aerosol I	mg/ml
	Compound X.....	10.0
	Sorbitan trioleate.....	13.5
	Trichlorofluoromethane.....	910.0
	Dichlorodifluoromethane.....	490.0
10	(i) Aerosol II	mg/ml
	Compound X.....	0.2
	Sorbitan trioleate.....	0.27
	Trichlorofluoromethane.....	70.0
15		280.0
	Dichlorodifluoromethane.....	1094.0
	(j) Aerosol III	mg/ml
	Compound X.....	2.5
20	Sorbitan trioleate.....	3.38
	Trichlorofluoromethane.....	67.5
	Dichlorodifluoromethane.....	1086.0
	Dichlorotetrafluoroethane.....	191.6
25	(k) Aerosol IV	mg/ml
	Compound X.....	2.5
	Soya lecithin.....	2.7
	Trichlorofluoromethane.....	67.5
	Dichlorodifluoromethane.....	1086.0
30	Dichlorotetrafluoroethane.....	191.6
	(l) Ointment	ml
	Compound X.....	40 mg

- 68 -

Ethanol.....	300 µl
Water.....	300 µl
1-Dodecylazacycloheptan-2-one.....	50 µl
Propylene glycol.....	to 1 ml

5

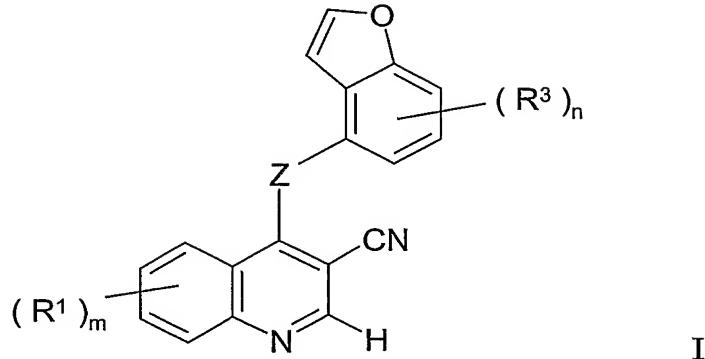
Note

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a)-(c) may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate. The aerosol formulations (h)-(k) 10 may be used in conjunction with standard, metered dose aerosol dispensers, and the suspending agents sorbitan trioleate and soya lecithin may be replaced by an alternative suspending agent such as sorbitan monooleate, sorbitan sesquioleate, polysorbate 80, polyglycerol oleate or oleic acid.

15

CLAIMS

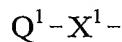
1. A quinoline derivative of the Formula I



5 wherein **Z** is an O, S, SO, SO₂, N(R²) or C(R²)₂ group, wherein each R² group, which may be the same or different, is hydrogen or (1-6C)alkyl;

m is 0, 1, 2, 3 or 4;

each **R¹ group**, which may be the same or different, is selected from halogeno, trifluoromethyl, cyano, isocyano, nitro, hydroxy, mercapto, amino, formyl, carboxy, 10 carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, (3-6C)alkenoylamino, N-(1-6C)alkyl-15 (3-6C)alkenoylamino, (3-6C)alkynoylamino, N-(1-6C)alkyl-(3-6C)alkynoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :



wherein X¹ is a direct bond or is selected from O, S, SO, SO₂, N(R⁴), CO, CH(OR⁴), 20 CON(R⁴), N(R⁴)CO, SO₂N(R⁴), N(R⁴)SO₂, OC(R⁴)₂, SC(R⁴)₂ and N(R⁴)C(R⁴)₂, wherein R⁴ is hydrogen or (1-6C)alkyl, and Q¹ is aryl, aryl-(1-6C)alkyl, (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl, or (R¹)_m is (1-3C)alkylenedioxy, and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R¹ substituent 25 are optionally separated by the insertion into the chain of a group selected from O, S, SO, SO₂, N(R⁵), CO, CH(OR⁵), CON(R⁵), N(R⁵)CO, SO₂N(R⁵), N(R⁵)SO₂, CH=CH and C≡C wherein

R^5 is hydrogen or (1-6C)alkyl or, when the inserted group is $N(R^5)$, R^5 may also be (2-6C)alkanoyl,

and wherein any $CH_2=CH-$ or $HC\equiv C-$ group within a R^1 substituent optionally bears at the terminal $CH_2=$ or $HC\equiv$ position a substituent selected from halogeno, carboxy, carbamoyl,

5 (1-6C)alkoxycarbonyl, N -(1-6C)alkylcarbamoyl, N,N -di-[(1-6C)alkyl]carbamoyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl and di-[(1-6C)alkyl]amino-(1-6C)alkyl or from a group of the formula :

$$Q^2-X^2-$$

wherein X^2 is a direct bond or is selected from CO and $N(R^6)CO$, wherein R^6 is hydrogen or

10 (1-6C)alkyl, and Q^2 is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, cyano, amino, carboxy, carbamoyl, (1-6C)alkoxy, (1-6C)alkylthio,

15 (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N -(1-6C)alkylcarbamoyl, N,N -di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamin, N -(1-6C)alkyl-(2-6C)alkanoylamin, N -(1-6C)alkylsulphamoyl, N,N -di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamin and N -(1-6C)alkyl-(1-6C)alkanesulphonylamin, or from a

20 group of the formula :

$$-X^3-Q^3$$

wherein X^3 is a direct bond or is selected from O , S , SO , SO_2 , $N(R^7)$, CO , $CH(OR^7)$,

$CON(R^7)CO$, $SO_2N(R^7)$, $N(R^7)SO_2$, $C(R^7)_2O$, $C(R^7)_2S$ and $N(R^7)C(R^7)_2$, wherein R^7 is

hydrogen or (1-6C)alkyl, and Q^3 is aryl, aryl-(1-6C)alkyl, (3-7C)cycloalkyl, (3-7C)cycloalkyl-

25 (1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any aryl, heteroaryl or heterocyclyl group within a substituent on R^1 optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl,

30 (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenylloxy, (2-6C)alkynylloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N -(1-6C)alkylcarbamoyl,

N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :

5

 $-X^4-R^8$

wherein X^4 is a direct bond or is selected from O and N(R^9), wherein R^9 is hydrogen or (1-6C)alkyl, and R^8 is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl or (1-6C)alkoxycarbonylamino-(1-6C)alkyl,

10 or from a group of the formula :

 $-X^5-Q^4$

wherein X^5 is a direct bond or is selected from O, N(R^{10}) and CO, wherein R^{10} is hydrogen or (1-6C)alkyl, and Q^4 is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same

15 or different, selected from halogeno, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl and (1-6C)alkoxy,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo or thioxo substituents;

n is 0, 1, 2 or 3; and

20 R^3 is halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino,

25 N-(1-6C)alkyl-(2-6C)alkanoylamino, (3-6C)alkenoylamino, N-(1-6C)alkyl-(3-6C)alkenoylamino, (3-6C)alkynoylamino, N-(1-6C)alkyl-(3-6C)alkynoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :

 $-X^6-R^{11}$

30 wherein X^6 is a direct bond or is selected from O and N(R^{12}), wherein R^{12} is hydrogen or (1-6C)alkyl, and R^{11} is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl or di-[(1-6C)alkyl]amino-(1-6C)alkyl, or from a group of the formula :

$$-X^7-Q^5$$

wherein X^7 is a direct bond or is selected from O, S, SO, SO₂, N(R¹³), CO, CH(OR¹³), CON(R¹³), N(R¹³)CO, SO₂N(R¹³), N(R¹³)SO₂, C(R¹³)₂O, C(R¹³)₂S and N(R¹³)C(R¹³)₂, wherein R¹³ is hydrogen or (1-6C)alkyl, and Q⁵ is aryl, aryl-(1-6C)alkyl, heteroaryl,

5 heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl and (1-6C)alkoxy, and any heterocyclyl group within Q⁵ optionally bears 1 or 2 oxo or thioxo substituents, or a pharmaceutically-acceptable salt thereof.

10

2. A quinoline derivative of the Formula I as claimed in claim 1 wherein m is 1 or 2, and each R¹ group, which may be the same or different, is selected from halogeno, trifluoromethyl, hydroxy, amino, carbamoyl, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, N-(1-6C)alkylcarbamoyl,

15 N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoylamino and N-(1-6C)alkyl-(2-6C)alkanoylamino, or from a group of the formula :

$$Q^1-X^1-$$

wherein X¹ is selected from O, N(R⁴), CON(R⁴), N(R⁴)CO and OC(R⁴)₂ wherein R⁴ is hydrogen or (1-6C)alkyl, and Q¹ is aryl, aryl-(1-6C)alkyl, cycloalkyl-(1-6C)alkyl, heteroaryl,

20 heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl, or X¹ is a direct bond and Q¹ is aryl-(1-6C)alkyl, cycloalkyl-(1-6C)alkyl, heteroaryl-(1-6C)alkyl or heterocyclyl-(1-6C)alkyl,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R¹ substituent are optionally separated by the insertion into the chain of a group selected from O, N(R⁵),

25 CON(R⁵), N(R⁵)CO, CH=CH and C≡C wherein R⁵ is hydrogen or (1-6C)alkyl, or, when the inserted group is N(R⁵), R⁵ may also be (2-6C)alkanoyl,

and wherein any CH₂ or CH₃ group within a R¹ substituent optionally bears on each said CH₂ or CH₃ group one or more halogeno groups or a substituent selected from hydroxy, amino, (1-6C)alkoxy, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino,

30 (2-6C)alkanoyloxy, (2-6C)alkanoylamino and N-(1-6C)alkyl-(2-6C)alkanoylamino, or from a group of the formula :

$$-X^3-Q^3$$

wherein X^3 is a direct bond or is selected from O , $N(R^6)$, $CON(R^7)$, $N(R^7)CO$ and $C(R^7)_2O$, wherein R^7 is hydrogen or (1-6C)alkyl, and Q^3 is heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any aryl, heteroaryl or heterocyclyl group within a substituent on R^1 5 optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, hydroxy, amino, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (1-6C)alkylsulphonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl and (2-6C)alkanoyl, or optionally bears 1 substituent selected from a group of the formula :

10 $-X^4-R^8$

wherein X^4 is a direct bond or is selected from O and $N(R^9)$, wherein R^9 is hydrogen or (1-6C)alkyl, and R^8 is hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl or (1-6C)alkoxycarbonylamino-(1-6C)alkyl, and from a 15 group of the formula :

$-X^5-Q^4$

wherein X^5 is a direct bond or is selected from O , $N(R^{10})$ and CO , wherein R^{10} is hydrogen or (1-6C)alkyl, and Q^4 is heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, (1-6C)alkyl and 20 (1-6C)alkoxy,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo substituents.

3. A quinoline derivative of the Formula I as claimed in claim 1 wherein R^1 substituents 25 may only be located at the 5-, 6- and/or 7-positions on the quinoline ring.

4. A quinoline derivative of the Formula I as claimed in claim 1 wherein :

Z is O or NH ;

30 m is 1 and the R^1 group is located at the 5-, 6- or 7-position or m is 2 and each R^1 group, which may be the same or different, is located at the 5- and 7-positions or at the 6- and 7-positions and R^1 is selected from hydroxy, amino, methyl, ethyl, propyl, butyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, pent-4-nyloxy, hex-5-nyloxy, methylamino, ethylamino, dimethylamino, diethylamino, acetamido, propionamido, 2-imidazol-1-ylethoxy,

2-(1,2,4-triazol-1-yl)ethoxy, tetrahydrofuran-3-yloxy, tetrahydropyran-4-yloxy,
2-pyrrolidin-1-yloxy, 3-pyrrolidin-1-ylpropoxy, 4-pyrrolidin-1-ylbutoxy,
pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-yloxy,
3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 4-morpholinobutoxy,

5 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-
4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy,
piperidin-3-yloxy, piperidin-4-yloxy, piperidin-3-ylmethoxy, piperidin-4-ylmethoxy,
2-piperidin-3-yloxy, 3-piperidin-3-ylpropoxy, 2-piperidin-4-yloxy,
3-piperidin-4-ylpropoxy, 2-homopiperidin-1-yloxy, 3-homopiperidin-1-ylpropoxy,

10 2-piperazin-1-yloxy, 3-piperazin-1-ylpropoxy, 4-piperazin-1-ylbutoxy,
2-homopiperazin-1-yloxy and 3-homopiperazin-1-ylpropoxy,
and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R¹ substituent
are optionally separated by the insertion into the chain of a group selected from O, NH,
N(Me), CH=CH and C≡C,

15 and wherein any CH₂ or CH₃ group within a R¹ substituent optionally bears on each
said CH₂ or CH₃ group one or more chloro groups or a substituent selected from hydroxy,
amino, methoxy, methylsulphonyl, methylamino, dimethylamino, diethylamino,
N-ethyl-N-methylamino, N-isopropyl-N-methylamino, N-methyl-N-propylamino and acetoxy;
and wherein any heteroaryl or heterocyclyl group within a substituent on R¹ optionally
20 bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro,
trifluoromethyl, hydroxy, amino, carbamoyl, methyl, ethyl, methoxy, N-methylcarbamoyl and
N,N-dimethylcarbamoyl and a pyrrolidin-2-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl or
homopiperazin-1-yl group within a R¹ substituent is optionally N-substituted with allyl,
methylsulphonyl, acetyl, 2-methoxyethyl, 3-methoxypropyl, cyanomethyl, 2-aminoethyl,
25 3-aminopropyl, 2-methylaminoethyl, 3-methylaminopropyl, 2-dimethylaminoethyl,
3-dimethylaminopropyl, 2-pyrrolidin-1-yethyl, 3-pyrrolidin-1-ylpropyl, 2-morpholinoethyl,
3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, 2-piperazin-1-yethyl or
3-piperazin-1-ylpropyl, the last 8 of which substituents each optionally bears 1 or 2
substituents, which may be the same or different, selected from fluoro, chloro, methyl and
30 methoxy,
and wherein any heterocyclyl group within a substituent on R¹ optionally bears 1 or 2
oxo substituents; and

n is 0 or 1 and the R³ group, if present, is located at the 3-, 5- or 6-position of the benzofuran-4-yl group and is selected from fluoro, chloro, bromo, trifluoromethyl, cyano, hydroxy, methyl, ethyl, vinyl, allyl, ethynyl, methoxy and ethoxy; or a pharmaceutically-acceptable acid-addition salt thereof.

5

5. A quinoline derivative of the Formula I as claimed in claim 1 wherein :

Z is O or NH;

m is 2 and the first R¹ group is a 6-methoxy group and the second R¹ group is located at the 7-position and is selected from 2-dimethylaminoethoxy, 3-dimethylaminoproxy,

- 10 4-dimethylaminobutoxy, 2-diethylaminoethoxy, 3-diethylaminoproxy,
4-diethylaminobutoxy, 2-diisopropylaminoethoxy, 3-diisopropylaminoproxy,
4-diisopropylaminobutoxy, 2-(N-isopropyl-N-methylamino)ethoxy,
3-(N-isopropyl-N-methylamino)prooxy, 4-(N-isopropyl-N-methylamino)butoxy,
2-(N-isobutyl-N-methylamino)ethoxy, 3-(N-isobutyl-N-methylamino)prooxy,
- 15 4-(N-isobutyl-N-methylamino)butoxy, 2-(N-allyl-N-methylamino)ethoxy,
3-(N-allyl-N-methylamino)prooxy, 2-(N-prop-2-ynylamino)ethoxy,
3-(N-prop-2-ynylamino)prooxy, 2-(N-methyl-N-prop-2-ynylamino)ethoxy,
3-(N-methyl-N-prop-2-ynylamino)prooxy, 2-pyrrolidin-1-yloxy,
3-pyrrolidin-1-ylprooxy, 4-pyrrolidin-1-ylbutoxy, pyrrolidin-3-yloxy,
- 20 N-methylpyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-yloxy,
3-pyrrolidin-2-ylprooxy, 2-morpholinoethoxy, 3-morpholinoproxy, 4-morpholinobutoxy,
2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-
4H-1,4-thiazin-4-yl)prooxy, 2-piperidinoethoxy, 3-piperidinoproxy, 4-piperidinobutoxy,
piperidin-3-yloxy, N-methylpiperidin-3-yloxy, piperidin-4-yloxy, N-methylpiperidin-4-yloxy,
- 25 piperidin-3-ylmethoxy, N-methylpiperidin-3-ylmethoxy,
N-cyanomethylpiperidin-3-ylmethoxy, piperidin-4-ylmethoxy,
N-methylpiperidin-4-ylmethoxy, N-cyanomethylpiperidin-4-ylmethoxy,
2-piperidin-3-yloxy, 2-(N-methylpiperidin-3-yl)ethoxy, 3-piperidin-3-ylprooxy,
3-(N-methylpiperidin-3-yl)prooxy, 2-piperidin-4-yloxy,
- 30 2-(N-methylpiperidin-4-yl)ethoxy, 3-piperidin-4-ylprooxy,
3-(N-methylpiperidin-4-yl)prooxy, 2-(4-hydroxypiperidin-1-yl)ethoxy,
3-(4-hydroxypiperidin-1-yl)prooxy, 4-(4-hydroxypiperidin-1-yl)butoxy,
2-homopiperidin-1-yloxy, 3-homopiperidin-1-ylprooxy, 4-homopiperidin-1-ylbutoxy,

2-(1,2,3,6-tetrahydropyridin-1-yl)ethoxy, 3-(1,2,3,6-tetrahydropyridin-1-yl)propoxy,
4-(1,2,3,6-tetrahydropyridin-1-yl)butoxy, 2-piperazin-1-ylethoxy,
2-(4-methylpiperazin-1-yl)ethoxy, 3-piperazin-1-ylpropoxy,
3-(4-methylpiperazin-1-yl)propoxy, 4-piperazin-1-ylbutoxy,
5 4-(4-methylpiperazin-1-yl)butoxy, 2-(4-allylpiperazin-1-yl)ethoxy,
3-(4-allylpiperazin-1-yl)propoxy, 4-(4-allylpiperazin-1-yl)butoxy,
2-(4-prop-2-ynylpiperazin-1-yl)ethoxy, 3-(4-prop-2-ynylpiperazin-1-yl)propoxy,
4-(4-prop-2-ynylpiperazin-1-yl)butoxy, 2-(4-methylsulphonylpiperazin-1-yl)ethoxy,
3-(4-methylsulphonylpiperazin-1-yl)propoxy, 4-(4-methylsulphonylpiperazin-1-yl)butoxy,
10 2-(4-acetyl)piperazin-1-yl)ethoxy, 3-(4-acetyl)piperazin-1-yl)propoxy,
4-(4-acetyl)piperazin-1-yl)butoxy, 2-[4-(2-fluoroethyl)piperazin-1-yl]ethoxy,
3-[4-(2-fluoroethyl)piperazin-1-yl]propoxy, 4-[4-(2-fluoroethyl)piperazin-1-yl]butoxy,
2-(4-cyanomethyl)piperazin-1-yl)ethoxy, 3-(4-cyanomethyl)piperazin-1-yl)propoxy,
4-(4-cyanomethyl)piperazin-1-yl)butoxy, 2-(2-piperazin-1-ylethoxy)ethoxy,
15 2-[2-(4-methyl)piperazin-1-yl)ethoxy]ethoxy, 2-chloroethoxy, 3-chloropropoxy,
4-chlorobutoxy, 2-methylsulphonylethoxy, 3-methylsulphonylpropoxy,
2-tetrahydropyran-4-ylethoxy, 3-tetrahydropyran-4-ylpropoxy, 2-pyrrol-1-ylethoxy,
3-pyrrol-1-ylpropoxy, 2-(2-pyridyloxy)ethoxy, 3-(2-pyridyloxy)propoxy,
2-(3-pyridyloxy)ethoxy, 3-(3-pyridyloxy)propoxy, 2-(4-pyridyloxy)ethoxy,
20 3-(4-pyridyloxy)propoxy, 2-pyridylmethoxy, 3-pyridylmethoxy and 4-pyridylmethoxy,
and wherein any CH_2 group within the second R^1 group that is attached to two carbon atoms optionally bears a hydroxy group on said CH_2 group,
and wherein any heteroaryl group within the second R^1 group optionally bears 1 or 2 substituents selected from chloro, cyano, hydroxy and methyl, and any heterocycl group
25 within the second R^1 group optionally bears 1 or 2 substituents selected from fluoro, hydroxy, methyl and oxo; and
 n is 0 or n is 1 and the R^3 group, if present, is located at the 5-, 6- or 7-position of the benzofuran-4-yl group and is selected from fluoro, chloro, bromo, iodo and cyano;
or a pharmaceutically-acceptable acid-addition salt thereof.

6. A quinoline derivative of the Formula I as claimed in claim 1 wherein :
Z is O or NH;

m is 2 and the first R¹ group is a 6-methoxy group and the second R¹ group is located at the 7-position and is selected from 2-dimethylaminoethoxy, 3-dimethylaminopropoxy, 4-dimethylaminobutoxy, 2-diethylaminoethoxy, 3-diethylaminopropoxy, 4-diethylaminobutoxy, 2-diisopropylaminoethoxy, 3-diisopropylaminopropoxy,

5 4-diisopropylaminobutoxy, 2-(N-isopropyl-N-methylamino)ethoxy, 3-(N-isopropyl-N-methylamino)propoxy, 4-(N-isopropyl-N-methylamino)butoxy, 2-(N-isobutyl-N-methylamino)ethoxy, 3-(N-isobutyl-N-methylamino)propoxy, 4-(N-isobutyl-N-methylamino)butoxy, 2-(N-allyl-N-methylamino)ethoxy, 3-(N-allyl-N-methylamino)propoxy, 2-(N-prop-2-ynylamino)ethoxy,

10 3-(N-prop-2-ynylamino)propoxy, 2-(N-methyl-N-prop-2-ynylamino)ethoxy, 3-(N-methyl-N-prop-2-ynylamino)propoxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 4-pyrrolidin-1-ylbutoxy, pyrrolidin-3-yloxy, N-methylpyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 4-morpholinobutoxy,

15 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy, piperidin-3-yloxy, N-methylpiperidin-3-yloxy, piperidin-4-yloxy, N-methylpiperidin-4-yloxy, piperidin-3-ylmethoxy, N-methylpiperidin-3-ylmethoxy, N-cyanomethylpiperidin-3-ylmethoxy, piperidin-4-ylmethoxy,

20 N-methylpiperidin-4-ylmethoxy, N-cyanomethylpiperidin-4-ylmethoxy, 2-piperidin-3-ylethoxy, 2-(N-methylpiperidin-3-yl)ethoxy, 3-piperidin-3-ylpropoxy, 3-(N-methylpiperidin-3-yl)propoxy, 2-piperidin-4-ylethoxy, 2-(N-methylpiperidin-4-yl)ethoxy, 3-piperidin-4-ylpropoxy, 3-(N-methylpiperidin-4-yl)propoxy, 2-homopiperidin-1-ylethoxy,

25 3-homopiperidin-1-ylpropoxy, 4-homopiperidin-1-ylbutoxy, 2-piperazin-1-ylethoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 3-piperazin-1-ylpropoxy, 3-(4-methylpiperazin-1-yl)propoxy, 4-piperazin-1-ylbutoxy, 4-(4-methylpiperazin-1-yl)butoxy, 2-(4-allylpiperazin-1-yl)ethoxy, 3-(4-allylpiperazin-1-yl)propoxy, 4-(4-allylpiperazin-1-yl)butoxy,

30 2-(4-methylsulphonylpiperazin-1-yl)ethoxy, 3-(4-methylsulphonylpiperazin-1-yl)propoxy, 4-(4-methylsulphonylpiperazin-1-yl)butoxy, 2-(4-acetylpirazin-1-yl)ethoxy, 3-(4-acetylpirazin-1-yl)propoxy, 4-(4-acetylpirazin-1-yl)butoxy, 2-(4-cyanomethylpiperazin-1-yl)ethoxy, 3-(4-cyanomethylpiperazin-1-yl)propoxy,

4-(4-cyanomethylpiperazin-1-yl)butoxy, 2-(2-piperazin-1-ylethoxy)ethoxy,
 2-[2-(4-methylpiperazin-1-yl)ethoxy]ethoxy, 2-chloroethoxy, 3-chloropropoxy,
 2-methylsulphonylethoxy, 3-methylsulphonylpropoxy, 2-tetrahydropyran-4-ylethoxy,
 3-tetrahydropyran-4-ylpropoxy, 2-pyrrol-1-ylethoxy, 3-pyrrol-1-ylpropoxy,
 5 2-(2-pyridyloxy)ethoxy, 3-(2-pyridyloxy)propoxy, 2-(3-pyridyloxy)ethoxy,
 3-(3-pyridyloxy)propoxy, 2-(4-pyridyloxy)ethoxy, 3-(4-pyridyloxy)propoxy,
 2-pyridylmethoxy, 3-pyridylmethoxy and 4-pyridylmethoxy,

and wherein any CH_2 group within the second R^1 group that is attached to two carbon atoms optionally bears a hydroxy group on said CH_2 group,

10 and wherein any heteroaryl group within the second R^1 group optionally bears 1 or 2 substituents selected from chloro, cyano, hydroxy and methyl, and any heterocyclyl group within the second R^1 group optionally bears 1 or 2 substituents selected from fluoro, hydroxy, methyl and oxo; and

n is 0 or n is 1 and the R^3 group, if present, is located at the 6-position of the 15 benzofuran-4-yl group and is selected from fluoro, chloro and bromo; or a pharmaceutically-acceptable acid-addition salt thereof.

7. A quinoline derivative of the Formula I as claimed in claim 1 wherein :

Z is NH ;

20 m is 2 and the first R^1 group is a 6-methoxy group and the second R^1 group is located at the 7-position and is selected from methoxy, ethoxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-(1,2,3,6-tetrahydropyridin-1-yl)ethoxy, 3-(1,2,3,6-tetrahydropyridin-1-yl)propoxy, 4-(1,2,3,6-tetrahydropyridin-1-yl)butoxy, 2-(4-hydroxypiperidin-1-yl)ethoxy, 3-(4-hydroxypiperidin-1-yl)propoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 4-(4-methylpiperazin-1-yl)butoxy, 3-(4-allylpiperazin-1-yl)propoxy, 3-(4-prop-2-ynylpiperazin-1-yl)propoxy, 30 3-(4-acetylpirazin-1-yl)propoxy, 4-(4-acetylpirazin-1-yl)butoxy, 3-[4-(2-fluoroethyl)piperazin-1-yl]propoxy, 2-(4-cyanomethylpiperazin-1-yl)ethoxy, 3-(4-cyanomethylpiperazin-1-yl)propoxy, 3-chloropropoxy, 4-chlorobutoxy, 2-methylsulphonylethoxy, 3-methylsulphonylpropoxy and 2-(2-methoxyethoxy)ethoxy; and

n is 0 or n is 1 and the R³ group, if present, is located at the 5- or 6-position of the benzofuranyl group and is selected from fluoro, chloro, bromo and iodo; or a pharmaceutically-acceptable acid-addition salt thereof.

5 8. A quinoline derivative of the Formula I as claimed in claim 1 wherein :

Z is O or NH;

m is 1 and the R¹ group is located at the 5-position and is selected from tetrahydrofuran-3-yloxy, tetrahydropyran-4-yloxy, tetrahydrothien-3-yloxy, 1,1-dioxotetrahydrothien-3-yloxy, tetrahydrothiopyran-4-yloxy,

10 1,1-dioxotetrahydrothiopyran-4-yloxy, N-methylazetidin-3-yloxy, N-ethylazetidin-3-yloxy, N-isopropylazetidin-3-yloxy, pyrrolidin-3-yloxy, N-methylpyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 3-piperidinyloxy, N-methylpiperidin-3-yloxy, 4-piperidinyloxy, N-methylpiperidin-4-yloxy, N-allylpiperidin-4-yloxy, N-prop-2-ynylpiperidin-4-yloxy, N-acetylpiperidin-4-yloxy, N-methylsulphonylpiperidin-4-yloxy,

15 N-(2-methoxyethyl)piperidin-4-yloxy, piperidin-3-ylmethoxy, N-methylpiperidin-3-ylmethoxy, piperidin-4-ylmethoxy, N-methylpiperidin-4-ylmethoxy, cyclobutyloxy, cyclopentyloxy and cyclohexyloxy,

or m is 2 and the first R¹ group is located at the 5-position and is selected from the group of substituents listed immediately above and the second R¹ group is located at the

20 7-position and is selected from hydroxy, methoxy, ethoxy, propoxy, isopropoxy, isobutoxy, 2-fluoroethoxy, 2,2,2-trifluoroethoxy, benzyloxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-piperidin-4-ylethoxy,

25 2-(N-methylpiperidin-4-yl)ethoxy, 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 3-(4-cyanomethylpiperazin-1-yl)propoxy, 2-[(2S)-2-carbamoylpyrrolidin-1-yl]ethoxy, 2-[(2S)-2-(N-methylcarbamoyl)pyrrolidin-1-yl]ethoxy,

30 2-[(2S)-2-(N,N-dimethylcarbamoyl)pyrrolidin-1-yl]ethoxy, 2-tetrahydropyran-4-ylethoxy, 2-hydroxyethoxy, 3-hydroxypropoxy, 2-methoxyethoxy, 3-methoxypropoxy, 2-methylsulphonylethoxy, 3-methylsulphonylpropoxy, 2-(2-methoxyethoxy)ethoxy,

piperidin-4-ylmethoxy, N-methylpiperidin-4-ylmethoxy, 2-(4-pyridyloxy)ethoxy, 2-pyridylmethoxy, 3-pyridylmethoxy, 4-pyridylmethoxy and 3-cyanopyrid-4-ylmethoxy; and wherein any CH₂ group within a R¹ substituent that is attached to two carbon atoms optionally bears a hydroxy group on said CH₂ group, and wherein any heterocyclyl group within a R¹ substituent optionally bears 1 or 2 oxo substituents, 5 and wherein any CH₂ group within a R¹ substituent that is attached to two carbon atoms optionally bears a hydroxy group on said CH₂ group; n is 0 or n is 1 and the R³ group, if present is located at the 3-, 5-, 6- or 7-position of the benzofuran-4-yl group and is selected from fluoro, chloro, bromo, trifluoromethyl, cyano, 10 methyl, ethyl, ethynyl, methoxy and ethoxy; or a pharmaceutically-acceptable acid-addition salt thereof.

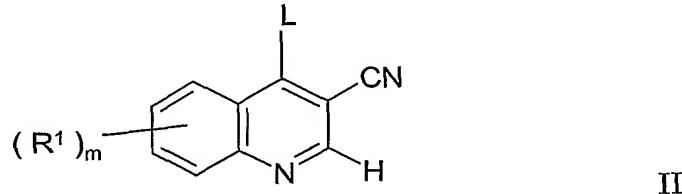
9. A quinoline derivative of the Formula I as claimed in claim 1 wherein : m is 2 and the first R¹ group is located at the 5-position and is selected from 15 tetrahydropyran-4-yloxy, N-methylpyrrolidin-3-yloxy, 4-piperidinyloxy, N-methylpiperidin-4-ylmethoxy, and the second R¹ is located at the 7-position and is selected from methoxy, benzyloxy, 2-pyrrolidin-1-yethoxy, 3-pyrrolidin-1-ylpropoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-(4-methylpiperazin- 20 1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy and 3-methylsulphonylpropoxy; n is 0 or n is 1 and the R³ group, if present, is located at the 6-position of the benzofuran-4-yl group and is selected from chloro and bromo; or a pharmaceutically-acceptable acid-addition salt thereof.

25 10. A quinoline derivative of the Formula I as claimed in claim 1 wherein : Z is NH; m is 1 and the R¹ group is located at the 5-position and is selected from tetrahydropyran-4-yloxy, 4-piperidinyloxy and N-methylpiperidin-4-yloxy, or m is 2 and the first R¹ group is located at the 5-position and is selected from 30 tetrahydropyran-4-yloxy, 4-piperidinyloxy and N-methylpiperidin-4-yloxy, and the second R¹ group is located at the 7-position and is selected from methoxy, ethoxy, propoxy, 3-pyrrolidin-1-ylpropoxy, 3-piperidinopropoxy, 3-morpholinopropoxy, 3-piperazin-1-ylpropoxy and 3-(4-methylpiperazin-1-yl)propoxy;

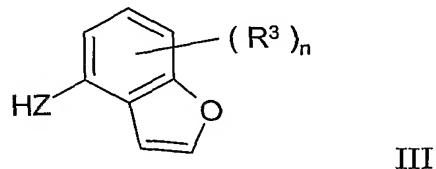
n is 0 or n is 1 and the R³ group, if present, is a chloro group located at the 5-position of the benzofuran-4-yl group;
or a pharmaceutically-acceptable acid-addition salt thereof.

5 11. A process for the preparation of a quinoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, according to claim 1 which comprises :-

(a) for the production of those compounds of the Formula I wherein Z is an O, S or N(R²) group, the reaction of a quinoline of the Formula II

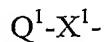


10 wherein L is a displaceable group and m and R¹ have any of the meanings defined in claim 1 except that any functional group is protected if necessary, with a compound of the Formula III

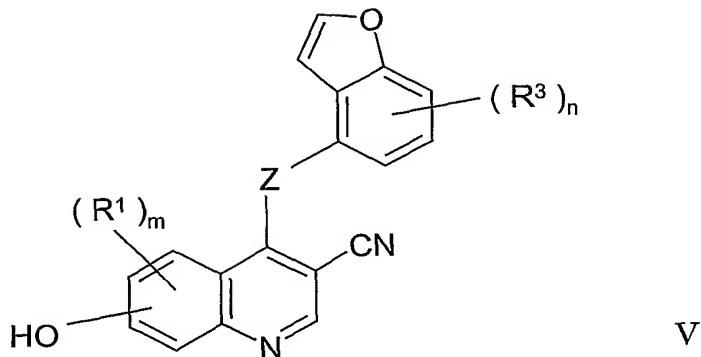


wherein Z is O, S, or N(R²) and n, R³ and R² have any of the meanings defined in claim 1 except that any functional group is protected if necessary, whereafter any protecting group that 15 is present is removed by conventional means;

(b) for the production of those compounds of the Formula I wherein at least one R¹ group is a group of the formula

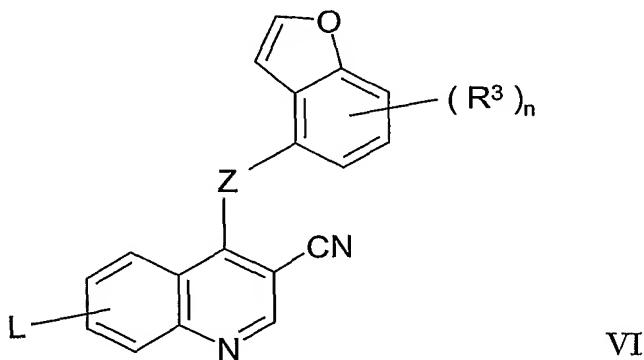


wherein Q¹ is an aryl-(1-6C)alkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl-(1-6C)alkyl or heterocyclyl-(1-6C)alkyl group or an optionally substituted alkyl group and X¹ is an oxygen atom, the coupling of a quinoline of the Formula V



wherein m, R¹, Z, n and R³ have any of the meanings defined in claim 1 except that any functional group is protected if necessary, with an appropriate alcohol wherein any functional group is protected if necessary whereafter any protecting group that is present is removed by 5 conventional means;

(c) for the production of those compounds of the Formula I wherein an R¹ group contains a (1-6C)alkoxy or substituted (1-6C)alkoxy group or a (1-6C)alkylamino or substituted (1-6C)alkylamino group, the reaction of a quinoline derivative of the Formula VI



10 wherein L is a displaceable group and Z, n and R³ have any of the meanings defined in claim 1 except that any functional group is protected if necessary, with an alcohol or amine as appropriate whereafter any protecting group that is present is removed by conventional means;

(d) for the production of those compounds of the Formula I wherein R¹ is an amino-substituted (1-6C)alkoxy group, the reaction of a compound of the Formula I wherein 15 R¹ is a halogeno-substituted (1-6C)alkoxy group with a heterocyclyl compound or an appropriate amine;

(e) for the production of those compounds of the Formula I wherein R¹ is a hydroxy group, the cleavage of a quinoline derivative of the Formula I wherein R¹ is a (1-6C)alkoxy or arylmethoxy group;

(f) for the production of those compounds of the Formula I wherein an R¹ group contains a primary or secondary amino group, the cleavage of the corresponding compound of the Formula I wherein the R¹ group contains a protected primary or secondary amino group;

(g) for the production of those compounds of the Formula I wherein an R¹ group

5 contains a (1-6C)alkoxy or substituted (1-6C)alkoxy group or a (1-6C)alkylamino or substituted (1-6C)alkylamino group, the alkylation of a quinoline derivative of the formula I wherein the R¹ group contains a hydroxy group or a primary or secondary amino group as appropriate;

(h) for the production of those compounds of the Formula I wherein R¹ is an

10 amino-hydroxy-disubstituted (1-6C)alkoxy group, the reaction of a compound of the Formula I wherein the R¹ group contains an epoxy-substituted (1-6C)alkoxy group with a heterocyclyl compound or an appropriate amine;

(i) for the production of those compounds of the Formula I wherein an R¹ group

15 contains a hydroxy group, the cleavage of the corresponding compound of the Formula I wherein the R¹ group contains a protected hydroxy group;

(j) for the production of those compounds of the Formula I wherein Z is a SO or SO₂ group, the oxidation of a compound of Formula I wherein Z is a S group; or

(k) the conversion of a compound of the Formula I wherein an R¹ or R³ substituent is a halogeno group into a further compound of the Formula I wherein the R¹ or R³ substituent is a

20 cyano, ethynyl or phenyl group;

and when a pharmaceutically-acceptable salt of a quinoline derivative of the Formula I is required, it may be obtained by reaction of said quinoline derivative with a suitable acid using a conventional procedure.

25 12. A pharmaceutical composition which comprises a quinoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, according to claim 1 in association with a pharmaceutically-acceptable diluent or carrier.

13. A quinoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof,

30 according to claim 1 for use in a method of treatment of the human or animal body by therapy.

14. The use of a quinoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, according to claim 1 in the manufacture of a medicament for use as an anti-invasive agent in the containment and/or treatment of solid tumour disease.

5 15. A method for producing an anti-invasive effect by the containment and/or treatment of solid tumour disease in a warm-blooded animal in need of such treatment which comprises administering to said animal an effective amount of a quinoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, according to claim 1.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 02/05535A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/4709 C07D405/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BEILSTEIN Data, PAJ, CHEM ABS Data, EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 43960 A (AMERICAN CYANAMID CO) 8 October 1998 (1998-10-08) cited in the application especially definitions of X the whole document ---	1-15
A	WO 00 68201 A (POYSER JEFFREY PHILIP ;TURNER PAUL (GB); BOYLE FRANCIS THOMAS (GB)) 16 November 2000 (2000-11-16) cited in the application see especially definitions of R9 the whole document ---	1-15
X	WO 00 18761 A (AMERICAN CYANAMID CO) 6 April 2000 (2000-04-06)	1-4, 11-15
Y	see especially claims 2,3,7, page 16, line 11 and page 23 ---	1-15
		-/-

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

5 March 2003

Date of mailing of the international search report

12/03/2003

Name and mailing address of the ISA

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Scruton-Evans, I

INTERNATIONAL SEARCH REPORT

Inte
nal Application No
PCT/GB 02/05535

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BOSCHELLI D H ET AL: "SYNTHESIS AND SRC KINASE INHIBITORY ACTIVITY OF A SERIES OF 4-PHENYLAMINO-3-QUINOLINECARBONITRILES" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 44, no. 5, 1 March 2001 (2001-03-01), pages 822-833, XP001105607 ISSN: 0022-2623 cited in the application the whole document ---	1-15
Y	BOSCHELLI D H ET AL: "OPTIMIZATION OF 4-PHENYLAMINO-3-QUINOLINECARBONITRILES AS POTENT INHIBITORS OF SRC KINASE ACTIVITY" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 44, no. 23, 8 November 2001 (2001-11-08), pages 3965-3977, XP001105608 ISSN: 0022-2623 cited in the application the whole document ---	1-15
Y	WANG Y D ET AL: "Inhibitors of Src tyrosine kinase: the preparation and structure-activity relationship of 4-anilino-3-cyanoquinolines and 4-anilinoquinazolines" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 10, no. 21, 6 November 2000 (2000-11-06), pages 2477-2480, XP004224243 ISSN: 0960-894X the whole document ---	1-15
E	WO 03 08409 A (ASTRAZENECA) 30 January 2003 (2003-01-30) the whole document -----	1-15

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 02/05535

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 15 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int'l Application No

PL 3 02/05535

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9843960	A 08-10-1998	AU 750906 B2		01-08-2002
		AU 6877798 A		22-10-1998
		CN 1259125 T		05-07-2000
		EP 0973746 A1		26-01-2000
		HU 0002112 A2		28-09-2000
		JP 2001519788 T		23-10-2001
		NO 994798 A		24-11-1999
		NZ 337782 A		27-04-2001
		PL 335999 A1		05-06-2000
		SK 135799 A3		16-05-2000
		TR 9902946 T2		21-03-2000
		WO 9843960 A1		08-10-1998
		ZA 9802771 A		01-10-1999
-----	-----	-----	-----	-----
WO 0068201	A 16-11-2000	AU 4589100 A		21-11-2000
		BG 106073 A		31-05-2002
		BR 0010391 A		02-07-2002
		CN 1365355 T		21-08-2002
		CZ 20013997 A3		13-02-2002
		EP 1178967 A1		13-02-2002
		WO 0068201 A1		16-11-2000
		HU 0201219 A2		28-09-2002
		JP 2002544196 T		24-12-2002
		NO 20015448 A		07-01-2002
		SK 16102001 A3		04-06-2002
		TR 200103186 T2		22-04-2002
-----	-----	-----	-----	-----
WO 0018761	A 06-04-2000	AU 6159399 A		17-04-2000
		BR 9914167 A		19-06-2001
		CA 2344169 A1		06-04-2000
		CN 1320121 T		31-10-2001
		CZ 20011038 A3		12-09-2001
		EP 1117659 A1		25-07-2001
		HU 0103520 A2		28-02-2002
		JP 2002525369 T		13-08-2002
		NO 20011575 A		28-05-2001
		PL 346934 A1		11-03-2002
		SK 4132001 A3		07-01-2002
		WO 0018761 A1		06-04-2000
-----	-----	-----	-----	-----
WO 0308409	A 30-01-2003	WO 03008409 A1		30-01-2003